VISION RESEARCH

A NATIONAL PLAN: 1978-1982

THE 1977 REPORT OF THE
NATIONAL ADVISORY EYE COUNCIL

Volume One

Summary

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service, National Institutes of Health

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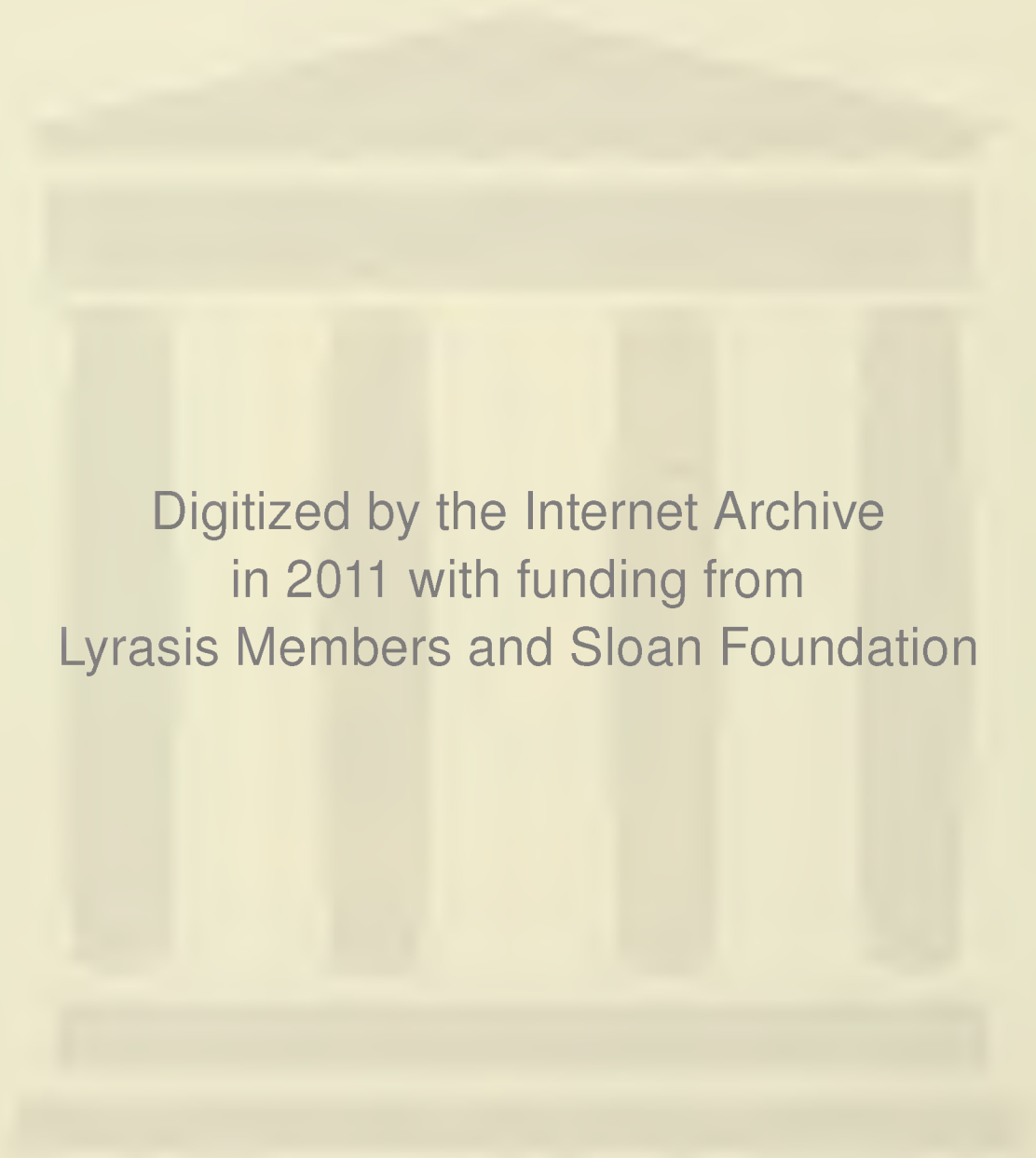
DHEW Publication No. (NIH) 78-1258



Foreword

THERE ARE NO primers for planning national biomedical research programs. At the National Institutes of Health, each component approaches research planning in its own way. The strategy and methods used vary according to the extent and nature of the disease problems being addressed; the state of the art in the prevention, diagnosis, and treatment of these disorders; the status of basic knowledge in the field and in related scientific disciplines; the numbers and types of trained researchers available; and the distinctive patterns of interaction that exist within the particular research community.

In vision research — for which the National Eye Institute is the primary source of support in the United States — the need for ongoing, comprehensive program planning at the national level is clear. The enormous magnitude of the problem of blindness and visual disability and the fact that there are many more opportunities for productive research than there are funds and manpower to carry them out require some system or plan for the rational allocation of available research resources to areas of the greatest need, importance, and promise.

Acceptance of the need for vision research program planning leads to the question of approach. Certainly, it is inadvisable for research planning to be carried out in isolation from the scientific community which it is expected to influence or to be imposed upon that community with a heavy hand. In the field of vision research — as in much of the rest of bioscience — there are far too many unknowns, and the scientific community's voluntary response to and support of planning goals, objectives, and priorities is essential. But neither, because of a desire to be universally acceptable, can the approach to planning be so restrained and lacking in detail as to be worthless either as a guide to scientists in preparing research proposals or to government managers in preparing budgets and making policy.

What is needed, then, is a reasonably balanced approach, one that derives from careful and detailed expert assessments of the extent of the problem; past accomplishments; current capabilities, needs and possible approaches; and the resources required for further advance. Based on this evaluation, priorities must be set; that is, from a large number of promising opportunities, the few which are believed most likely to result in significant further advances should be singled out. Vision research planning should also be used as a means of public accounting for past achievements and future prospects.

Of course, research planning will not guarantee success. At any time, an unforeseen problem may stymie one highly promising line of inquiry, while an unexpected discovery may open an entirely new field. Biomedical research planning may be fallible, but if its structure is flexible enough to accommodate the unplanned, yet strong enough to keep true to its objectives, then planning may be an effective in-

strument for facilitating the advancement of scientific knowledge and the conquest of disease.

This is the approach the National Advisory Eye Council has tried to take in preparing *Vision Research — A National Plan*. The Council, a legislatively mandated group of 12 citizens who represent basic and clinical vision research, eye care, or the public at large, advises the National Eye Institute Director and his staff on the awarding of grants and on program and policy development. We believe that the plan presented in this three-volume report is sufficiently detailed to be meaningful yet elastic enough to encompass whatever new developments may spring from the creativity and ingenuity of the vision research community and science at large. Because more than 160 leading representatives of that community were closely involved in the preparation of this plan, we are confident that it does address the most important needs and opportunities that exist in vision research today. By focusing attention on the high priority areas of basic and applied research identified by these experts and by stressing their relevance to the solution of important visual health problems, we hope that this plan will have a beneficial influence on the course of vision research and help lead us to the eventual elimination of the major eye and visual disorders which plague our Nation.

This plan is based upon a previous Council report, *Vision Research Program Planning*, published in 1975. In that publication, the Council presented its views on the background, rationale, and principles of national vision research program planning. Each of the National Eye Institute's major programs was reviewed, and a select list of recommended priorities in each was presented. The enthusiastic response to this initial effort from vision research scientists, government officials, members of Congress, and the public — along with some helpful criticism — has prompted the preparation of this second report — one that is considerably more detailed and far-ranging than the first, but which retains the original's essential philosophy, principles, and approach.

Volume One contains a summary of the Council's latest findings and recommendations with respect to each of the National Eye Institute's programs and for vision research training and career development. A discussion of important cross-cutting policy and administrative issues is also presented. The complete reports of six Panels of experts convened by the Council to assist in the evaluation of the National Eye Institute's research and research training programs in detail are included in Volume Two. Each report is followed by a series of tables that show the number of additional projects and the financial and manpower resources that are required to carry out the priority recommendations. Finally, extensive data on vision research support in the United States that served as an important information resource for the Panels and the Council are included in Volume Three.

Taken as a whole, these volumes represent an attempt by a concerned group of scientists and citizens to come to terms in an organized way with a national health problem of massive proportions. Through this plan, we hope to speed the solution of this problem, thereby hastening the alleviation of the pain, suffering, and economic and social hardship caused by visual disorders.

A. EDWARD MAUMENEE, M.D.
Chairman
Program Planning Subcommittee
National Advisory Eye Council

Introduction

THE EYE AND its afflictions have through the ages been shrouded in superstition and myth. In art and literature, blindness is a frequent tragic theme, a metaphor for ignorance, or a fateful punishment for wrongdoing. Blind people have at various times in history been thought of as either cursed or blessed, have been alternately shunned or pitied, and have even been believed to have miraculous powers for either good or evil.

Such attitudes and prejudices have evolved into a kind of modern mythology about the eye and blindness which even today overshadows more factual assessments of visual impairment as a multidimensional public health, social, and economic problem. Blindness is still greatly feared: public opinion polls have shown that it is held second only to cancer as the most dreaded of human afflictions. And, despite intensive public education programs, there is still widespread ignorance and misunderstanding of blindness and its causes and of the means available for its prevention and cure.

It is even possible that such attitudes have to some extent impeded research on vision and its disorders. Although much good has been done in the past to provide assistance to those who are already blind, only recently has interest grown in finding new and better ways to prevent and cure blindness, particularly that caused by chronic disorders. And, just recently has the plight of the millions who have partial vision, but do not qualify for benefits due the blind, begun to be fully appreciated.

It is this growing awareness, both of the promise of research and of the full extent of the problem, that in the past quarter century — and especially during the last decade, following the creation of the National Eye Institute — has helped propel the field of vision research to the forefront of biomedical science. Today, investigations into the normal and abnormal structure and function of the visual system are not only advancing knowledge of vision and visual disorders but are providing new understanding of basic life processes and systemic diseases. By studying the eye, for example, we are learning how to modulate the effects of diabetes on vision while adding to general knowledge about this devastating and highly prevalent disease. By studying the effects of early sensory deprivation on the developing visual system, we are gaining important knowledge of the requirements for the normal development of the central nervous system. By testing drugs against ocular viral infections, we are creating the forerunners of a new class of compounds that may effect cures for a number of diseases for which there is presently no hope. By studying the effects of aging on the protein structure of the human lens, we are gaining important insights into the very nature of the aging process.

As the principal source of support for vision research in the United States and perhaps the world, the National Eye Institute is responsible for providing leadership

in this field, for helping maintain the high quality standards that have been established, and for assuring that the primary objective of such studies continues to be the improvement of health and the alleviation of human suffering.

In recognition of this obligation and of the fact that there will never be enough funds to support all worthwhile research proposals, the National Advisory Eye Council, the principal consultative body to the National Eye Institute, in 1974 embarked upon an unprecedented attempt to evaluate the Nation's vision research effort and to develop a structure for priority setting that would focus public and scientific attention on the most pressing problems and most promising opportunities in this field while assuring the continued free exercise of scientific creativity. The Council's report, *Vision Research Program Planning*, published in 1975, documented the need for program planning during a period of fluctuating health research budgets and at a time when increasing emphasis was being placed on the importance of accountability to the public for research expeditures.

The response by the scientific community, higher levels of government — including the Congress — and the public to the Council's first report has been most favorable and enthusiastic. Encouraged by this reaction, the Council began planning a second report which would explore more thoroughly a number of issues that had been raised before and to discuss several new topics which are currently of great interest and concern. With the rationale and principles of vision research program planning well established, the Council believed that by involving additional representatives of the vision research community in the planning process, more definitive plans could be developed that could serve as detailed guidelines for the development of the National Eye Institute's program within the traditional pattern of investigator-initiated research.

The result is this document, *Vision Research — A National Plan*, a product of two years of work by the Council and six Panels of scientific advisors, assisted by the staff of the National Eye Institute and nongovernment consultants in program planning. In preparing this second report, the Council has been mindful of the constructive comments and criticisms it received concerning the first report and has tried to respond to as many of these as possible. In the present report, for instance, the Council has tried to be more explicit in presenting the background from which its recommendations and research priorities have been derived. Wherever possible, the extent of the problem has been documented, the state of the art described, program goals and research objectives outlined, ongoing research evaluated in terms of its relevancy to these goals and objectives, a broad range of research needs and possible approaches discussed, the selection of research priorities from among these justified, and estimates provided of the level of effort and financial resources required to carry them out. The effective presentation of such detailed information has required a more complex format than was used in the first report; it is one that should serve in future planning activities, with appropriate modifications as needed.

The Council's first report has been of great value to the National Eye Institute staff in formulating policy and in carrying out the day-to-day management of NEI programs. It has also proved to be a quite valuable resource for responding to requests for program information from higher governmental levels and from the public and has increased our capability for responding in a timely and straightforward fashion to evolving and emerging national policies concerning governmental support of biomedical science. In general, as a result of the Council's program planning efforts, we are today in an excellent position to take stock of past accomplishments, formulate specific goals and objectives for the immediate and long-range future, use to best advantage the resources that are currently available, and present a strong justification for future support.

This new national research plan should serve to strengthen these National Eye Institute capabilities and, because of the broad base of expert knowledge and opin-

ion upon which it is founded, should also be of use to other organizations, both public and private, whose objective is the prevention and eradication of blindness and visual impairment and disability through research.

Only with time will the full measure of the Council's program planning activities be taken. But we are now able to begin evaluating the impact of the first report, and judging from initial impressions, the long-range effects of program planning on the course of vision research and on the rate of progress in this field may well be considerable. The National Eye Institute intends to continue assessing the results of program planning and to provide future assistance to the Council in this essential and praiseworthy activity.

CARL KUPFER, M.D.
Director
National Eye Institute

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Executive Summary

THE FOLLOWING IS a summary of the National Advisory Eye Council's recommendations for the future development of the National Eye Institute's program in each of the five major fields of vision research and in research training. These recommendations derive from detailed assessments of the state of the art in each of these fields and from expert analyses of the major needs and opportunities that now exist in vision research.

Summaries of the reports of the six Panels of distinguished scientists that assisted the Council in preparing this national plan are presented in Chapter 5 of this volume, but for a full account of the background and rationale for these recommendations and for details of the recommendations themselves, the reader is referred to Volume Two in which the unabridged Panel reports appear.

The Council also hopes that these reports will serve individual scientists as a guide to choosing subjects for investigation and thereby hasten the solution of critical problems related to blinding and disabling eye disorders which burden such a large segment of our Nation's population.

Summary of Research Priorities

Retinal and Choroidal Diseases

1. Pursue vigorously studies in the following areas:

   - The specific anatomy, biochemistry, and physiology of the retinal photoreceptor cells and of the underlying pigment epithelium. These studies should focus on both normal animal and human tissue as well as tissue from dystrophic animals and from humans with retinal disease.
   - Application of techniques from such basic research disciplines as psychophysics and electrophysiology to the diagnosis and understanding of retinal and choroidal disease.
   - Macular degeneration, especially its relationship to age changes in Bruch's membrane (which separates the retina and choroid), to the formation of abnormal new blood vessels, and to the metabolism of the pigment epithelium-photoreceptor complex.
   - The characteristics of the blood circulation within the retina and choroid, and the cause of the changes which occur in diabetes mellitus and other retinal vascular diseases.

- The mechanisms which normally keep the retina attached to the posterior wall of the eye, and the structural and functional derangements which may contribute to retinal detachment.
- The neurophysiology of retinal organization and visual adaptation, especially in the primate.

2. Give attention to the following neglected areas of research:
   - Normal and disease processes of the uveal tract.
   - The composition, structure, and pathology of the vitreous humor.
   - Normal and pathological processes in developmental and hereditary disorders.
   - Myopia, its development and possible control, including an intensive study of the normal process of eye growth.
   - The nature and origin of eye tumors as well as new therapeutic approaches.
   - Disorders of the eye induced by toxic substances and other environmental factors.
   - Low vision, especially improved and new ways to enable maximal use of the residual vision of partially sighted patients.
   - Vision substitutes to provide mobility aids for blind patients.
   - Retinal regeneration and transplantation.
3. Make intensive efforts to obtain and develop appropriate animal models of retinal and choroidal disease.
4. Develop techniques for safe retinal and choroidal biopsy, especially to aid research on uveitis, developmental and hereditary disorders, and inflammatory disorders.
5. Devise diagnostic techniques for inflammatory disorders in the absence of direct biopsy.
6. Facilitate the search for pathological, biochemical, and physiological correlates of ocular disorders by developing a national registry in cooperation with local eye banks that collect, preserve, and distribute eyes for which a thorough record of their clinical course has been compiled.
7. Collect and evaluate comparative clinical data on the use of vitrectomy, the surgical removal of diseased, opaque vitreous from the eye.
8. Establish a mechanism for interagency coordination of vision research in general and, in particular, research on retinal and choroidal diseases, particularly with regard to toxic and environmental hazards.

Corneal Diseases

1. Determine the roles of viruses, particularly herpes virus, their antigenic products, and the host inflammatory responses to these viruses in corneal disease.
2. Develop effective methods to treat corneal viral diseases and to modify the host response.
3. Study the composition, chemical and physical characteristics, and drainage of tears in health and disease.

4. Describe the immune mechanism in tear gland dysfunction.
    - The nature and origin of eye tumors as well as new therapeutic approaches.
5. Study blink mechanisms and blink stimulation in reference to preventing damage to the chronically dry eye.
6. Study the healthy and damaged epithelium, the outermost layer of the cornea, which is especially vulnerable to disease or injury.
7. Develop drugs and other means of preventing or reversing corneal scarring or opacities and preventing blood vessel infiltration of corneal tissue.
8. Develop, evaluate, and compare new and existing means of drug delivery to ocular tissues.
9. Determine genetic influences on drug reactions in the cornea.
10. Determine the effects of new contact lens materials upon corneal physiology and metabolism and establish criteria for the safety, efficacy, and uses of new lens materials.
11. Determine the effectiveness and safety of orthokeratology, a technique to remold the shape of the cornea with contact lenses, to correct nearsightedness.
12. Determine the capacity of the endothelium (the fragile layer which lines the inside of the cornea and helps maintain its proper hydration) to regenerate, define the characteristics of endothelial disease, and study the effects of various drugs and methods of corneal preservation and of different surgical and transplantation procedures upon the endothelium.
13. Establish the usefulness of specular microscopy and fluorophotometry in determining corneal tissue changes in the living eye as well as the suitability of donor corneal tissue for transplantation.
14. Investigate means of improving the outcome of corneal transplantation by applying modern immunological techniques.
15. Improve means of diagnosing and treating ocular, lid, and orbital carcinomas and pseudotumors.

Cataract

1. Conduct further studies of the structure, chemistry, and light transmission properties of the normal lens.
2. Develop methods of tissue culture of human lens and lens cells.
3. Through a nationwide cooperative research group increase study of human senile cataract:
    - Apply new biochemical and biophysical techniques to the study of senile cataract
    - Develop methods for tissue culture of senile cataract
    - Design electronic equipment for documenting cataract development.
4. Study changes in lens carbohydrate and lipid metabolism with aging and cataract.

5. Study the efficacy and long-term effect of intraocular lens implantation following cataract surgery through animal studies and a large-scale clinical trial.
6. Search for epidemiologic data for clues to the cause of cataract and/or possible risk factors associated with its development.
7. Study further the chemical pathways by which diabetes causes or accelerates cataract formation.
8. Further develop and test in humans new chemical inhibitors of diabetic cataract formation.
9. Study further the effect of viruses in inducing certain forms of cataract.
10. Study inborn errors of metabolism which cause cataract.
11. Determine the dose/response characteristics of drugs which induce cataracts in humans.
12. Investigate the effect of ultraviolet light on the lenses of laboratory animals and humans.
13. Further investigate cataracts occurring secondary to other eye disorders such as uveitis, inflammation, and retinitis pigmentosa.
14. Investigate the causes of congenitally dislocated lenses and study their effect on the normal visual development of young children.
15. Investigate the relationships between the ciliary body and the lens, particularly in relation to aging and presbyopia, and their effects upon the retina.
16. Study optical problems associated with cataract and aphakia, their effect on normal visual development, and improved means of optical rehabilitation.

Glaucoma

1. Establish the relationship of genetic markers to the development of various types of glaucoma.
2. Determine whether glaucoma affects Blacks or other racial and ethnic groups more frequently, earlier in life, and/or more severely.
3. Improve methods for diagnostic prediction of angle-closure glaucoma and learn why people differ in their response to medical and surgical treatment for this condition.
4. Describe the manner in which the vitreous body is involved in angle-closure glaucoma and its complications.
5. Determine to what degree prostaglandins are involved in glaucomas occurring as a result of inflammation and injury in human eyes.
6. In order to provide better treatment, clarify how aqueous outflow is obstructed in secondary glaucoma, particularly that attributable to uveitis.
7. Clarify the basic mechanism of glaucoma associated with the exfoliation syndrome—a condition in which fine, gray particles are seen on the cornea, lens, and elsewhere in the eye — with the aim of better treatment and possibly prevention of glaucoma.

8. Develop an animal model for neovascular glaucoma in man and conduct experimental research on the mechanisms involved in the formation of new, abnormal blood vessels on the iris which block aqueous outflow and precipitate this condition.

9. Develop a primate animal model of chronic glaucoma for life-long investigation and stereophotographic documentation of changes induced in the appearance of the optic nerve head. Make subsequent correlations with laboratory tissue studies and explore how much individual variation there may be in susceptibility to injury by a given pressure.

10. Evaluate through prospective, controlled clinical research the risk to vision from treatment of systemic hypertension in patients with glaucoma.

11. Establish factors or tests that may indicate varying susceptibility of individual optic nerves to chronically elevated intraocular pressure. These factors may have predictive value and could serve as a guide to the amount of treatment needed in individual cases.

12. Clarify the cause of low tension glaucoma.

13. Ascertain the relative influences of physical factors and of metabolic processes in controlling aqueous humor outflow. This may lead to improved treatment and possibly even to prevention of some forms of glaucoma.

14. Develop better low risk means for measuring and monitoring the rate of aqueous humor formation in patients and in monkeys.

15. Obtain a complete understanding of the mechanism by which carbonic anhydrase inhibitors (commonly administered orally to help control glaucoma) influence aqueous formation, and explain why these drugs fail to reduce aqueous formation when topically administered.

16. Find new drugs that increase the rate of aqueous formation for potential application in the treatment of excessive hypotony (abnormally low pressure), such as that associated with choroidal detachment.

17. Increase understanding of how metabolic factors in the aqueous outflow channels may be altered in disease, how outflow regulation may be affected by hormones and drugs, and how these tissues may be involved in governing resistance to aqueous outflow.

18. Explain how detachment of the choroid and ciliary body may reduce formation of aqueous humor.

19. Establish whether cyclic variation in intraocular pressure results from variation in aqueous formation or in resistance to outflow, and establish more exactly whether this is in response to hormonal, neural, or other influences.

20. Devise a harmless device for continuously monitoring intraocular pressure in patients for many types of clinical glaucoma research.

21. Determine in which types of eyes subject to angle-closure glaucoma that treatment with miotic eyedrops acts favorably, causing opening and widening of the angle, and in which types of eyes the same miotic eyedrops act unfavorably, aggravating the shallowing of the anterior chamber and causing the angle to close.

22. Appraise the value of laser photocoagulation of new-formed vessels in the front part of the eye and of the retina in the treatment and prevention of

neovascular glaucoma in cases of diabetic retinopathy and of occlusion of central retinal vessels.

23. Conduct basic and clinical research aimed at improving the results of filtration surgery for glaucoma in children and young adults.
24. Clarify the basis for cataract formation after glaucoma operations.

Sensory and Motor Disorders of Vision

1. Study factors which regulate the development of the mammalian visual system and analyze the mechanisms which lead to the formation of highly organized visual pathways.
2. Study the effects of experimental strabismus on the structure and physiology of the visual nervous system in cats and monkeys.
3. Determine the periods in human development of greatest susceptibility to strabismic amblyopia and evaluate the usefulness of visual training and drugs in reversing this condition.
4. Develop and breed animal strains with congenital strabismus and related abnormalities.
5. Apply psychophysical techniques to the improved diagnosis of strabismic amblyopia.
6. Scientifically study and compare surgical and other therapies for strabismus.
7. Study eye muscle mechanics and eye rotation in strabismus.
8. Determine the cause and development of congenital nystagmus and other uncontrolled eye movements.
9. Design eye muscle prostheses to improve control of these disorders.
10. Develop and test drugs that act on the central nervous system to control abnormal eye movements.
11. Develop mathematical models of eye movement and test models of visual brain disease by computer simulation.
12. Compile reliable statistics on the incidence of eye movement disorders.
13. Study the chemical neurotransmitters of the retina and central nervous system.
14. Determine the basis of selectivity of higher visual neurons.
15. Determine the biochemical basis of plasticity in the visual cortex.
16. Apply visual psychophysical techniques to improving clinical diagnosis of retinal and sensorimotor disorders.
17. Improve the use and interpretation of electrical testing of visual nervous system function.
18. Continue development of optical electronic and mechanical visual substitutions and aid devices.
19. Evaluate the effectiveness of visual aids in facilitating mobility and education.
20. Develop training and educational methods for the visually handicapped.

Vision Research Training

1. Sustain the quality of the vision research environment through stable and consistent support of vision research training.
2. Assure that research training in the basic sciences related to vision continues to be adequately supported.
3. Foster training of both basic scientists and clinicians in a clinical research setting to focus attention on the most pressing disease problems and to assure the quality of clinical research.
4. Review applications for individual fellowships several times each year and establish a system of advanced funding so that resources are assured for all approved applications scheduled to be funded.
5. Increase the number of Academic Investigator Awards which help individuals establish themselves as independent investigators, and to help fill the great need for trained clinical investigators, remove the limitations on the number of awards per institution.
6. Encourage applications for Special Visual Sciences Research Awards by reorienting the review process so that there is greater recognition of the needs and limited experience of novice investigators and by adding a professional salary component not to exceed $15,000 to the present award base of $10,000.
7. Encourage training and support of basic scientists who are interested in and qualified to work in research related to the prevention of visual disorders.
8. Improve administrative procedures to facilitate the attainment of the National Eye Institute's research training goals and objectives.

Budget

To carry out the foregoing priorities, the Council recommends that a total of $118,648,000 and 210 positions be appropriated to the National Eye Institute in fiscal year 1978, with additional annual increments that lead to a recommended $199,882,000 and 280 positions for FY 1982. (See Tables 1 and 2.) The recommended level of funding for 1978 will support a total of 441 additional research projects. Though this represents a substantial increase over 1977, it does not allow for the support of several hundred other research projects which the National Advisory Eye Council and its consultants considered important but which could not be accommodated within the limits of the FY 1978 budget request.

Table 1
National Advisory Eye Council
Budget by Program
(Dollars in Thousands)

	FY 1977		FY 1978	
	Positions	Amount	Positions	Amount
Retinal and Choroidal Diseases		$23,125		$ 50,342
Corneal Diseases		7,586		13,421
Cataract		5,524		10,310
Glaucoma		7,692		13,524
Sensory and Motor Disorders of Vision		10,259		18,210
Intramural Laboratory and Clinical Research	(89)	7,098	(135)	9,136
Direct Operations	(36)	1,740	(45)	2,607
Program Management	(27)	976	(30)	1,098
Total	(152)	$64,000	(210)	$118,648

Table 2
National Advisory Eye Council
Budget by Mechanism
(Dollars in Thousands)

	FY 1977		FY 1978	
	Projects/ *Positions*	Amount	Projects/ *Positions*	Amount
Research Project Grants	632	$ 41,012	1,089	$ 75,264
Specialized Clinical Research Center Grants	8	1,394	34	9,113
Research Contracts	55	3,522	99	9,452
Core Center Grants	17	2,698	26	4,074
Research Career Development Awards	36	920	59	1,539
Research Training Grants	182	4,640	297	6,365
Intramural Laboratory and Clinical Research	*89*	7,098	*135*	9,136
Direct Operations	*36*	1,740	*45*	2,607
Program Management	*27*	976	*30*	1,098
Total	*152*	$ 64,000	*210*	$118,648

It should be noted that the projected five-year budget levels off in FY 1980 and includes little more than projected cost of living increases for the last two years. This reflects the Council's determination that a research budget of $171,853,000 in 1980 will allow the National Eye Institute to take maximum advantage of the priority research opportunities that currently exist in vision research.

FY 1979		FY 1980		FY 1981		FY 1982	
Positions	Amount	Positions	Amount	Positions	Amount	Positions	Amount
	$ 62,722		$ 77,466		$ 83,305		$ 89,969
	16,105		19,326		20,872		22,542
	12,063		14,114		15,243		16,462
	15,553		17,886		19,317		20,862
	21,942		25,083		27,010		29,091
(140)	10,865	(150)	13,465	(155)	14,650	(160)	15,243
(50)	2,920	(55)	3,184	(60)	3,662	(70)	4,105
(35)	1,208	(40)	1,329	(45)	1,462	(50)	1,608
(225)	$143,378	(245)	$171,853	(260)	$185,521	(280)	$199,882

FY 1979		FY 1980		FY 1981		FY 1982	
Projects/ *Positions*	Amount	Projects/ *Positions*	Amount	Projects/ *Positions*	Amount	Projects/ *Positions*	Amount
1,238	$ 90,440	1,401	$107,857	1,462	$115,425	1,516	$124,263
44	12,849	55	16,366	63	18,002	69	19,442
108	10,793	134	12,893	136	14,003	146	15,287
30	4,659	34	5,124	37	5,715	40	6,258
80	2,006	98	2,469	108	2,703	119	2,986
363	7,638	436	9,166	471	9,899	509	10,690
140	10,865	*150*	13,465	*155*	14,650	*160*	15,243
50	2,920	*55*	3,184	*60*	3,662	*70*	4,105
35	1,208	*40*	1,329	*45*	1,462	*50*	1,608
225	$143,378	*245*	$171,853	*260*	$185,521	*280*	$199,882

The recommended additional research projects were drawn directly from the priority recommendations of the Council's program Panels. (See Table 3 and the detailed Project and Resource Tables in Volume Two of this report.) In preparing the budget estimates, new projects intended as research grants were assigned an average total unit cost of $69,000 in FY 1978 and added to the FY 1977 base. The number of projects identified for support under research and development contracts was constrained both by considerations of the appropriate use of this mechanism in accord with NEI policies (see Chapter 2, *Implementation of Program Priorities*) and by the extraordinary amount of time and NEI staff necessary to administer these awards. Because the NEI uses contracts primarily to support clinical trials and specialized research resources, most of the recommended contract projects are of this type. These projects were assigned an average unit cost of $100,000 for FY 1978 and added to the FY 1977 base.

Proposed clinical research projects that seemed to be interrelated and complementary and suited for a highly structured research environment as set forth in current NEI guidelines for specialized clinical research centers were clustered together and identified for support through this mechanism. These centers were assigned an average unit cost of from $200,000 to $400,000 in FY 1978 and added to the FY 1977 base.

Table 3
National Advisory Eye Council
Resource Requirements
by Extramural Program
and Mechanism
FY 1978
(Dollars in Thousands)

	Research Grants		Specialized Clinical Research Centers	
	No.	Amt.	No.	Amt.
Retinal and Choroidal Diseases				
Estimated Support FY 1977	264	$17,054	2	$ 235
Additional Requirements FY 1978	236	17,363	15	4,624
Estimated Total Support FY 1978	500	$34,417	17	$4,859
Corneal Diseases				
Estimated Support FY 1977	84	$ 5,439	2	$ 401
Additional Requirements FY 1978	62	4,640	2	710
Estimated Total Support FY 1978	146	$10,079	4	$1,111
Cataract				
Estimated Support FY 1977	68	$ 4,465	1	$ 150
Additional Requirements FY 1978	37	2,838	2	700
Estimated Total Support FY 1978	105	$ 7,303	3	$ 850
Glaucoma				
Estimated Support FY 1977	83	$ 5,421	2	$ 458
Additional Requirements FY 1978	58	4,410	2	685
Estimated Total Support FY 1978	141	$ 9,831	4	$1,143
Sensory and Motor Disorders of Vision				
Estimated Support FY 1977	133	$ 8,633	1	$ 150
Additional Requirements FY 1978	64	5,001	5	1,000
Estimated Total Support FY 1978	197	$13,634	6	$1,150
All Extramural Programs				
Estimated Support FY 1977	632	$41,012	8	$1,394
Additional Requirements FY 1978	457	34,252	26	7,719
Estimated Total Support FY 1978	1,089	$75,264	34	$9,113

The Council believes that sufficient research manpower exists to carry out the projects included in the FY 1978 budget. On several past occasions, when the vision research community knew that there would be sufficient funds available, there was an abrupt increase in the number of high quality research grant applications submitted to the National Eye Institute (see Chapter 4, Table 7). For example, between FY 1971 and FY 1973, the first actual operational years of the National Eye Institute, the number of grant applications submitted to the Institute which were approved increased by 74 percent as a result of additional funds that were made available. As a result of the 28 percent increase in funds provided to the National Eye Institute in FY 1977, the number of approved grant applications increased 32 percent in that year, and the funding rate for approved grants was only about 54 percent. By making the conservative assumption that the rate of increase in approved grant applications for FY 1978 will be the same as for FY 1977, the Institute should have a wide selection of high quality options for allocating a $118 million budget.

Included in the proposed budget are funding increases for the direct operations of the National Eye Institute. These will accommodate costs associated with increased personnel requirements, provide funds necessary to cover inflation, and allow for some expansion in the Institute's administrative activities. Added funds should be provided to the NEI intramural research program for expanded activities in the Institute's five major research programs and to prepare for the new NIH Ambulatory Care Research Facility, expected to open in FY 1981.

Research Contracts		Core Centers		Research Career Awards		Research Training		
No.	Amt.	No.	Amt.	No.	Amt.	No.	Amt.	Total
53	$3,403	3	$ 311	19	$ 489	71	$1,633	$ 23,125
20	3,432	5	983	7	185	42	630	27,217
73	$6,835	8	$1,294	26	$ 674	113	$2,263	$ 50,342
1	$ 28	3	$ 548	4	$ 100	51	$1,070	$ 7,586
0	0	3	110	5	135	16	240	5,835
1	$ 28	6	$ 658	9	$ 235	67	$1,310	$ 13,421
0	$ 0	4	$ 509	3	$ 73	12	$ 327	$ 5,524
13	1,000	0	106	2	52	6	90	4,786
13	$1,000	4	$ 615	5	$ 125	18	$ 417	$ 10,310
1	$ 91	4	$ 833	3	$ 85	32	$ 804	$ 7,692
4	428	0	74	2	55	12	180	5,832
5	$ 519	4	$ 907	5	$ 140	44	$ 984	$ 13,524
0	$ 0	3	$ 497	7	$ 173	16	$ 806	$ 10,259
7	1,070	1	103	7	192	39	585	7,951
7	$1,070	4	$ 600	14	$ 365	55	$1,391	$ 18,210
55	$3,522	17	$2,698	36	$ 920	182	$4,640	$ 54,186
44	5,930	9	1,376	23	619	115	1,725	51,621
99	$9,452	26	$4,074	59	$1,539	297	$6,365	$105,807

With budget increases of the size recommended here, it is imperative that additional staff be made available to the National Eye Institute. This principle has been recognized in the past by the Senate Appropriations Committee. For instance, in its report on the FY 1977 DHEW appropriation request the Committee stated:

> *In fact, it would be wise program management to provide additional personnel to those programs for which the Committee has allowed additional funds.*

National Eye Institute position projections are also supported by a zero-base analysis of all National Institutes of Health manpower requirements. This analysis demonstrates that, even with 60 additional positions, the National Eye Institute still would have the smallest intramural research program at the National Institutes of Health and a higher productivity in most areas of the administration of its extramural awards than other components of the National Institutes of Health.

2

Implementation of Program Priorities

IN ITS FIRST report, *Vision Research Program Planning*, the National Advisory Eye Council concluded that, for the most part, the direction and scope of vision research in the United States were oriented appropriately toward the needs of society. However, the Council recommended that some "modest redirection" of this effort be attempted in order to make vision research even more responsive to the public's desire for improved eye care and health. The National Eye Institute was advised to pursue this redirection by actively disseminating the Council's report to the vision research community and to the general public and relying upon individual investigators to initiate projects in the areas of need and opportunity which the Council identified. More vigorous methods of implementing the Council's recommendations, such as the earmarking of specific funds for awards in special emphasis areas, were judged not in keeping with the largely unpredictable pace and pattern of scientific advance and were therefore considered inappropriate.

In this, its second program planning report, the Council reaffirms its view that the NEI should in general continue its "gentle" approach to promoting research in accordance with identified priorities. However, the Council also believes that, in selected cases, it is now both appropriate and desirable for NEI staff to expand and intensify its implementation efforts.

Most important, this program plan should be used by the National Advisory Eye Council and the National Eye Institute staff as a basis upon which to make judgments of program relevance concerning individual grant applications. In addition, the following activities should be undertaken:

- Publication in the widely-read *NIH Guide for Grants and Contracts* and leading vision science journals of announcements which encourage investigators to submit grant proposals in specific areas of research.
- Organization and sponsorship of workshops, symposia, and other discussion forums in which particular vision research needs and opportunities can be defined further and made more widely known.
- Identification of high priority, clinically relevant research opportunities that can be best taken advantage of through the support of cooperative clinical trials and specialized clinical research centers.
- Support, through research contracts, of selected research resources such as animal model breeding and distribution and instrumentation development and evaluation.

Through active communication with the research community, and by responsible program management, the National Eye Institute can do much to accelerate progress in vision research.

Recommendations

Investigator-Initiated Research

Investigator-initiated research should continue to be the mainstay of the National Eye Institute's program. Because the outcome of most laboratory and clinical research cannot be fully specified in advance, the vision research community must be allowed considerable freedom to exercise its expertise and best judgment in attacking the myriad problems that must be overcome if significant advances in combatting disabling eye diseases and preventing blindness are to continue. Thus, the first priority of the NEI must be to nurture investigator-initiated research, primarily by means of research project grants.

Vision Research Centers

The NEI should expand its support for the development and operation of vision research centers. This would do much to facilitate the implementation of the research priorities set forth in this report, especially where a richer interchange between the clinical milieu and the world of laboratory research is needed. In sponsoring these centers, the NEI should rely heavily on clusters of individual research project grants but should also utilize other support mechanisms where appropriate, for example, "core" grants, specialized clinical research center grants, institutional and individual fellowships, and research contracts.

This concept of a vision research center, that is, a research/patient care/education setting in which an array of individual research project grants and other types of awards are welded into a cohesive, multifaceted, and interactive program focused on a specific class of visual system disorders, has much to commend it. By promoting this concept, the NEI can help sustain the activities of the present major foci of vision research and help create new ones. It can also ensure that the individual projects which constitute the centers undergo rigorous scientific review at regular intervals in a way that does not subject the entire center to disruptive "all or nothing" funding considerations.

Research Contracts

The NEI should continue to limit its use of research contracts to the support of (1) multi-institutional, controlled clinical trials of significant new eye care and diagnostic procedures, (2) the maintenance and distribution of animal models of human visual disorders which are important to the national research effort but not readily available from commercial sources, and (3) the development and evaluation of unique instruments for use in vision research and eye care. In general, research contracts should be utilized only for activities of the highest program priority and then only when the steps required for attaining a desired objective can be specified in advance and in great detail.

Research Training and Career Development

The NEI should continue to foster the research training and career development of individuals interested in making the study of the visual system their principal vocation. Clearly, it will be impossible for the NEI to achieve its program goals if there is not a steady infusion of new, highly skilled, independent investigators into the vision research community. The NEI should, therefore, maintain a broad spectrum of award types keyed to the various stages in a scientist's maturation from beginning trainee to independent investigator. The NEI should also continuously monitor the relative need for individuals to receive support through these various types of awards and reallocate available funds from time to time as necessary. Particular attention should be given to broadening the use of the Academic Investigator Award (see Chapter 5, *Summaries of the Panel Reports, Vision Research Training* section). Among its other attributes, this award seems to be a near-ideal mechanism for enabling postresidency clinicians to participate in a guided research experience and to acquire in depth exposure to the kinds of scientific concepts and methods which are the hallmark of high-quality laboratory research.

Interaction Between Vision Science and Other Disciplines

Because the study of the visual system requires—and offers unique opportunities for—the application of the concepts and methods of other scientific disciplines, the NEI should continue to promote interdiscipline and multidiscipline research activities. The various types of awards for research training and career development are an excellent mechanism for this purpose, center grants are another. Through these various means, vision scientists can benefit from conceptual and technical advances in fields such as biochemistry, immunology, and biostatistics, to name but a few. Investigators in such disciplines can be encouraged to exploit the special characteristics of the visual system to study biological processes which are significant not only to eye care but also to other areas of medicine.

Intramural Research

The National Eye Institute's intramural program is a major national resource for research and research training in vision. When the new Ambulatory Care Research Facility (ACRF) now under construction at NIH is completed, the potential of the intramural program will increase greatly. The new clinical research facilities which the ACRF will make available will permit NEI to place even more emphasis on direct clinical research training activities than it does at present. Mid-career and senior investigators from the vision research community at large will also have more opportunities to spend sabbaticals at NIH in order to take advantage of the unique research opportunities and training facilities that will exist there. The NEI is therefore urged to continue its efforts to foster a strong research program within its intramural laboratories and clinic.

Peer Review and Program Management

The National Eye Institute should continue to rely upon peer review for evaluation of the scientific merit of research grant applications and contract

proposals. In order to ensure high quality and impartial technical appraisal of these requests for funds, the initial review groups (the Study Sections of NIH's Division of Research Grants in the case of research project grant applications) should remain as insulated as possible from concerns about program priorities and availability of funds.

By contrast, the National Advisory Eye Council should continue to concern itself not only with the adequacy of the initial reviewers' assessments of the merit of grant applications but also with determining the program relevance of individual grant applications and contract projects. This report and subsequent updatings should provide the conceptual framework upon which these assessments will be made.

By working against a backdrop of such specific Council actions and the program recommendations contained in this report, the NEI Director and his staff will be in an excellent position to make the final de ermination of a project's suitability for funding.

This tripartite process of award selection—review by Study Sections and other initial review groups for scientific merit, review by the Council for both scientific merit and program relevance, and final consideration and decision by NEI staff—assures the impartial and effective administration of NEI programs as well as the aggressive pursuit of national goals for the prevention and cure of major disorders affecting the eyes and visual system.

Program Planning and Evaluation

The NEI staff, in collaboration with the National Advisory Eye Council and other consultants, should continue to engage in vision research program planning and evaluation following the publication of this report. Because vision science is advancing so rapidly and the opportunities for payoff in terms of improved eye care are so numerous, this report should be updated and augmented in selected areas over the next four years in order to furnish the scientific community with timely, expert assessments of the most critical needs and opportunities for important new studies of the visual system. Such a process will also provide the Council and staff with sound guidance for carrying out their responsiblilties.

Emphasis should be placed on workshops, symposia, and special evaluation projects as means for attaining the requisite planning and evaluative information. The results of these activities should be published and disseminated broadly to the scientific community and, whenever appropriate, to the general public.

The NEI and Council should also publish an annual statistical analysis of NEI's program including additional pertinent data concerning visual system disorders and vision research that may become available. These reports should also document the progress that has been made in attaining program goals through implementation of the program priorities identified in this report. Five years from now, the National Advisory Eye Council should prepare and publish a third comprehensive analysis of the prevailing research needs and opportunities in vision research and a reassessment of all program priorities.

Responsibilities of NEI at the Health Research/Health Care Interface

The NEI should play an active role in assuring timely and effective introduction into the health care system of research results that may be applied to the

improved prevention, detection, diagnosis, and treatment of visual system disorders and to the rehabilitation of patients afflicted with blindness or other severe visual impairments. Steeply rising health care costs and wide disparities in health care quality and availability are evidence of major weaknesses in the Nation's health care system. Although biomedical research in general and vision research in particular clearly cannot single-handedly solve major national health care problems, the Congress and citizen groups are looking increasingly to the research community for leadership. The NEI should respond to this call.

As the world's principal source of support for vision research, the National Eye Institute, with the assistance of the National Advisory Eye Council, should take the initiative in fostering the translation and assimilation of research results into eye care. Furthermore, leading organizations interested in eye care and vision research such as the American Academy of Ophthalmology; American Association of Ophthalmology; American Academy of Optometry; American Optometric Association; Research to Prevent Blindness, Inc.; the National Society for the Prevention of Blindness; Friends of Eye Research, Rehabilitation, and Treatment; Fight for Sight, Inc.; and the American Foundation for the Blind—to name but a few—should be encouraged to participate fully in this activity.

In carrying out this expanded mission, the NEI should not be diverted from its primary purpose of fostering and supporting vision research. Therefore, it is mandatory that any major new responsibility should be supported through the addition of specific manpower and dollar resources to the NEI budget. Also, a new focal point should be established within the NEI organization to administer these new programs. Further discussion of this topic may be found in Chapter 7, *NEI Program and Management Issues.*

3

Background for Planning

THE STATISTICAL BACKGROUND and philosophical basis for vision research program planning is summarized in this and the following chapter. First, the National Eye Institute's five major programs are briefly described and their organization into subprograms discussed. Available data on the incidence, prevalence, and cost of the national problem of visual disorders are reviewed next. This is followed by a discussion of the process by which the National Advisory Eye Council conducts program planning, including planning principles, guidelines, and organization. The chapter concludes with an analysis of preliminary information on the progress to date in achieving planning goals.

National Eye Institute Programs

The groups of priorities for vision research presented in Chapter 1 and the Panel reports summarized in Chapter 5 correspond to the five major programs of the National Eye Institute. Each of these programs, described briefly below, encompasses basic and applied research on a large number of related eye and visual disorders. Many parts of the eye referred to in the program descriptions and elsewhere in this report can be identified in Figure 1.

Retinal and Choroidal Diseases

Most blindness and visual disability in the United States is caused by disorders of the *retina*, the light-sensitive tissue that lines the back of the eye. Closely related to the retina and helping nourish it is the underlying blood vessel layer, known as the *choroid*. Because of the proximity and interrelationship of these two structures, diseases affecting one usually involve the other. Unfortunately, for most retinal and choroidal diseases, there is neither means of cure or prevention. Progress against these disorders has been severely impeded by lack of knowledge of the fundamental processes underlying retinal and choroidal function.

In response to this need, the National Eye Institute is conducting and supporting basic and applied studies to elucidate the structure and function of the retina in health and disease. NEI-fostered investigations include studies of the structure and metabolism of the photoreceptor cells and their relationship to the underlying *pigment epithelium;* the mechanism of the retina's response to light and the initial proc-

essing of visual information that is transmitted to the visual centers of the brain; inflammation of the uveal tract of the eye consisting of the *iris*, choroid, and *ciliary body*; and of the *vitreous humor*, the clear gel that fills the center of the eye and which assumes importance in a number of ocular disorders.

The National Eye Institute also supports studies which are aimed at understanding such major causes of blindness as developmental and hereditary disorders of the retina; diabetic retinopathy and other vascular and circulatory abnormalities; myopia; tumors; diseases of the *macula* the central, high visual acuity area of the retina; retinal detachment; and inflammatory disorders, including uveitis. A number of clinical trials of the effects of treatment in certain retinal diseases, most notably diabetic retinopathy, are underway.

Corneal Diseases

Included within this program are diseases of the *cornea*, the transparent structure at the front of the eye that acts as a powerful lens, and of the external ocular structures, including the *conjunctiva* and lids. Corneal diseases occur frequently and are perhaps the leading cause of blindness worldwide. They are also, as a group, the most painful of eye disorders. One of the most difficult corneal diseases to treat is that caused by the herpes simplex virus. Often characterized by periodic acute recurrences, herpes simplex infections of the cornea account for more sickness and loss of vision than any other corneal infection in Western countries. Other conditions of concern in this program are inflammatory disorders of the cornea and external eye; dry eyes and tear abnormalities; disorders of the corneal epithelium; refractive problems and contact lenses; corneal edema, dystrophies, and inherited disorders; corneal transplantation and injury and repair of the corneal stroma; and tumors and other problems of the lids, conjunctiva, and orbit.

Research supported by the National Eye Institute related to corneal diseases includes studies of immunologic mechanisms, corneal opacification, edema, and improved means of drug delivery. Other important areas of corneal research include epidemiologic investigations, studies of the tear film, and tumor virology and immunology.

Cataract

A cataract is an opacity of the normally clear *lens* of the eye which interferes with vision. Although cataract surgery is one of the most successful operations performed, this condition remains among the leading causes of blindness in the United States. For this reason, the National Eye Institute is emphasizing research aimed at the prevention and nonsurgical treatment of cataract.

The NEI's cataract research program is concerned with a number of different types of cataract of varying etiology, including aging; diabetes; and congenital, metabolic, and genetic factors. Also of interest are cataracts occurring secondary to injury, radiation, and other eye disorders; dislocated lenses; and accommodation and optical problems of cataract and aphakia. Considerable attention is being given to studies of the chemistry and biophysics of the normal lens.

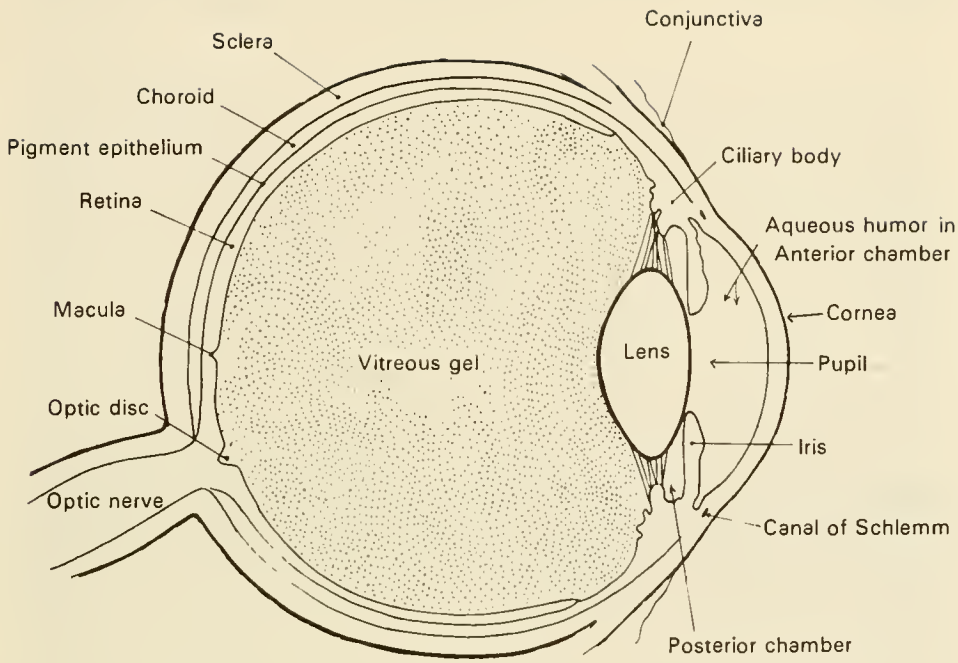

Figure 1. Cross section of the human eye.

Glaucoma

This disease is characterized by an elevation of pressure within the eye caused by a buildup of the *aqueous humor*, which is produced by the ciliary body to nourish the cornea and lens. This fluid drains from the eye through the *canal of Schlemm*. Obstruction of aqueous outflow is followed by damage to the *optic nerve* and subsequent loss of vision. The numerous forms of glaucoma have diverse etiologies and include primary and secondary types. However, research concerns common to all the glaucomas are optic nerve and vision changes, the hydrodynamics of the aqueous humor, and methods of medical and surgical treatment.

Sensory and Motor Disorders of Vision

This program encompasses a broad range of studies concerned with the structure and function of the neural pathways from the retina to the brain, the central processing of visual information, visual perception, optical properties of the eye, functioning of the *pupil*, and control of the ocular muscles. A large number of congenital, developmental, and degenerative abnormalities affect the visual sensorimotor system, but three disorders are of primary concern: strabismus, amblyopia, and nystagmus. These are frequent causes of visual impairment among children which may persist for life. Of particular interest are studies of the normal development of visual capacity in the infant and of the effects of early sensory deprivation on the development of visual function.

Subprograms

To facilitate program analysis and planning, each of the NEI's programs is divided into several subprograms, some of which are further subdivided into areas.

One of the Panels' first tasks was to consider carefully the existing structure of the National Eye Institute's programs to determine if the taxonomy was consistent with the present state of scientific knowledge and interest and if it provided a suitable framework for the Panels' investigations and reports. After considerable discussion, four of the Panels adopted new program classifications, and the fifth, *Sensory and Motor Disorders of Vision*, although essentially retaining the existing classification, chose to concentrate on five research topics within three of the subprograms which they considered deserving of special emphasis.

In Table 1, the subprograms adopted for use in this plan may be compared with those in the Council's 1975 report. The rationale for these changes is discussed in the unabridged Panel reports in Volume Two, but one reason for change was the Panels' desire to convey the importance of maintaining a balance between basic and applied research and to demonstrate the essential interrelationship of both approaches in the conquest of blinding and disabling eye diseases. This is especially evident in the new classification of the *Retinal and Choroidal Diseases* program in which the first seven subprograms are listed under the heading Problem Areas and Specific Disorders, while the next five are grouped under Development, Structure, and Function as Related to Disease. Throughout this Panel's report, reference is made to the interdependence of research targeted at specific eye disorders and fundamental studies of normal and abnormal retinal and choroidal structure and function.

Another reason for revising the subprogram classification was to emphasize the number and variety of disease and research problems with which a program may be concerned. For example, the Foreword to the *Cataract* Panel report in Volume Two states, ". . . a more specific delineation of subprograms better identifies the problem areas and may help attract researchers from other areas of medicine to cataract research."

A third reason for restructuring a program was the need to achieve a framework for planning that truly reflects the characteristics of a particular group of diseases. For instance, some NEI programs encompass several disorders which, although they affect a single ocular tissue, differ markedly as to cause, underlying mechanisms, means of diagnosis, clinical features, and therapeutic approach. Other programs are concerned with a more homogenous group of disorders, for example, *Glaucoma*. The revised organization of this program recognizes the diverse etiology of the various forms of glaucoma while stressing the common concerns of research on these several types: the effects of elevated intraocular pressure on the optic nerve, the control of the production and outflow of aqueous humor, and medical and surgical treatments aimed at reducing pressure within the eye.

Although traditional classifications of ocular disease and research have influenced the structure of the NEI programs, to some extent it reflects the collective interests and viewpoints of a great number of Panel members and consultants. Although the Council believes that the new system is scientifically valid and clearly emphasizes current major health problems and needs, it is important that this classification be periodically reexamined and revised if necessary, for the NEI program structure must be kept relevant to current problems and needs and to the latest developments in vision research.

Among the five programs, there are obvious areas of mutual concern and even overlap. For example, the ocular effects of diabetes are highlighted in both the

Retinal and Choroidal Diseases and *Cataract* programs. Congenital and developmental eye disorders are common to all five programs, although they are not specifically identified as a subprogram under *Glaucoma*. Developmental problems are, however, discussed in great detail in the etiology section of the *Glaucoma* Panel's report.

Not only common research concerns but the actual relationships among ocular disorders affecting different parts of the eye are stressed in the Panel reports. For example, secondary glaucoma is a frequent consequence of ocular inflammation, particularly that affecting the uveal tract. An increased incidence of cataract is associated with the inherited retinal degenerative disorder, retinitis pigmentosa, and permanent damage to the central visual pathways may be caused by early visual deprivation due to either congenital cataract or corneal opacities. Optical problems of the eye are discussed from different viewpoints in the *Retinal and Choroidal Diseases, Cataract,* and *Sensory and Motor Disorders of Vision* reports. Throughout each of the Panel reports in Volume Two, there are references to sections of the other reports where similar topics are discussed. In addition, the Index to that volume helps to cross-reference related topics.

Because of these shared problems and concerns, progress in one area of vision research may well lead to advances in another. This points to the need for improved communication among scientists in the various specialized fields of vision research and for increased collaboration among such individuals in investigations of mutual interest.

Table 1
National Eye Institute Program Structure

1975	1977
Retinal and Choroidal Diseases	
	Problem Areas and Specific Disorders
A. Development, Structure, Function, and Degeneration	A. Developmental and Hereditary Disorders
1. Choroid, Pigment Epithelium, and Related Disorders	B. Diabetic Retinopathy and Other Vascular and Circulatory Abnormalities
2. Visual Pigments, Photoreceptors, and and Visual Transduction Disorders	C. Myopia
3. Retinal Information Processing and Associated Disorders	D. Tumors
4. Developmental and Degenerative Disorders	E. Macular Diseases
B. Vascular and Circulatory Abnormalities — Including Disturbances in Blood Vessel Formation	F. Retinal Detachment
	G. Inflammatory Disorders
C. Inflammatory Diseases	Development, Structure, and Function as Related to Disease
D. Macular Diseases	H. Uveal Tract
E. Retinal Detachment and Vitreous Abnormalities	I. Vitreous Humor
F. Tumors	J. Visual Cells and Pigment Epithelium
	K. Retinal Organization and Visual Adaptation
	L. Special Areas of Future Interest • Toxic and Environmental Disorders • Low Vision • Retinal Regeneration and Transplantation • Tissue Acquisition and Distribution: Human Donor Eyes and Animal Models
Corneal Diseases	
A. Development, Structure, Function, and Degeneration	A. External Ocular Infections and Inflammatory Diseases
B. Inflammatory Diseases — Including Infectious Diseases and Allergy	B. Dry Eyes and Tear Abnormalities, Epithelial Disorders, and Drug Delivery
C. Trauma and Wound Healing — Including Transplantation	C. Refractive Problems and Contact Lenses
D. Tears and Corneal Tear Film	D. Corneal Edema, Dystrophies, and Inherited Disorders
E. Tumors	E. Corneal Transplantation and Stromal Injury and Repair
	F. Tumors and Other Lid, Conjunctival, and Orbital Problems

Cataract

A. Congenital Cataract and Developmental Abnormalities of the Lens	A. The Normal Lens
B. Lens Structure and Function and Metabolic, Toxic, and Traumatic Cataract	B. Senile or Degenerative Cataract
C. Degenerative (Senile) Cataract	C. Diabetic Cataract
	D. Congenital, Metabolic, and Genetic Cataracts
	E. Cataracts Induced By Drugs and Radiation and Occurring Secondary to Other Eye Disorders
	F. Dislocated Lens
	G. Accommodation and Optical Problems of Cataract and Aphakia

Glaucoma

A. Developmental Glaucoma	A. Etiology of Glaucoma
B. Primary Glaucoma — Including Intraocular Pressure Regulation	B. Optic Nerve and Vision Changes in Glaucoma
1. Open-Angle Glaucoma	C. Hydrodynamics of the Eye
2. Closed-Angle Glaucoma	D. Medical and Surgical Treatment of Glaucoma
C. Secondary Glaucoma	

Sensory and Motor Disorders of Vision

A. Congenital, Developmental, and Degenerative Abnormalities	A. Congenital, Developmental, and Degenerative Abnormalities
B. Oculomotor Disorders	B. Strabismus and Other Oculomotor Disorders
1. Strabismus	1. Strabismus and Amblyopia
2. Oculomotor Control	2. Disorders Affecting the Control of Eye Movements
C. Optical and Pupillary Disorders	C. Optical and Pupillary Disorders
D. Visual Sensory and Perceptual Disorders	D. Visual Sensory and Perceptual Disorders
1. Neural Mechanisms	1. Neural Mechanisms
2. Psychophysical Functions	2. Psychophysical Functions
3. Electrophysiological Techniques Applicable to Man	3. Electrophysiological Techniques Applicable to Man
E. Sensory and Motor Disorders Related to Specific Disease Processes	E. Sensory and Motor Disorders Related to Specific Disease Processes
1. Vascular and Circulatory Abnormalities	1. Vascular and Circulatory Abnormalities
2. Inflammatory Diseases	2. Inflammatory Diseases
3. Metabolic, Toxic, and Traumatic Disorders	3. Metabolic, Toxic, and Traumatic Disorders
4. Tumors	4. Tumors
F. Rehabilitation	F. Rehabilitation

Extent of the Problem

Any consideration of health research needs and priorities must begin with an assessment of the magnitude of the disease problem being addressed according to whatever measures may be available. For a comprehensive and quantitative overview of the national impact of visual disorders, the Council sought reliable statistics based upon well-designed population surveys of the extent and costs of eye diseases and blindness. To a large extent, we have relied upon data prepared for the National Eye Institute by the consulting firm Westat, Incorporated.[1] The Westat report is a review, analysis, and synthesis of existing data gathered from a variety of sources on the incidence, prevalence, and costs of visual disorders in the United States.

Its major findings are:

- Over 10 million people — 1 of every 20 in the United States — suffer from significant impairment of vision which cannot be further improved by corrective lenses.
- Of these, 1.5 million have such severe impairment that they are unable to read ordinary newsprint, even with glasses.
- Of those severely impaired, approximately 500,000 are legally blind.
- Each year, more than 3.7 million new cases of eye disorders are diagnosed.
- Approximately 2 million eye injuries occur annually.
- Eye conditions necessitate over 31 million visits for professional care or treatment each year.
- In 1972, the latest year for which statistics were available, the direct costs of eye care in the United States totalled approximately $3.6 billion. The indirect costs, estimated lost earnings, of eye disorders exceeded $1.5 billion a year. Therefore, the total economic cost of visual disorders and disability in the United States exceeded $5 billion. Taking inflation into account, the current comparable cost would be approximately $7 billion.

The causes of visual impairment and blindness are presented in Table 2 according to three degrees of impairment: impaired vision, severe visual impairment, and legal blindness. In Table 3, these figures have been grouped according to their relevance to the five major programs of the National Eye Institute with percentages assigned accordingly.

Since publication of the Westat report, the following additional information has become available:

- Eye disorders are outranked only by arthritis and cardiovascular diseases as a leading cause of limited activity among persons 65 years and older. Approximately 1.7 million people are limited in their daily activities because of visual impairment. Over one-half of these people would have otherwise been working or keeping house.[2]

[1]Westat, Inc: *Summary and Critique of Available Data on the Prevalence and Economic and Social Costs of Visual Disorders and Disabilities.* Rockville, MD, 16 February, 1976.

[2]National Center for Health Statistics: Limitation of Activity Due to Chronic Conditions, United States, 1974. *Vital and Health Statistics*, Series 10, Number 111, US DHEW Publ No (HRA) 77-1537, Washington, DC, 1977.

Table 2

Estimates of Prevalence of Impairment from Visual Disorders[1] United States, 1972

(Numbers in Thousands)

Type of Eye Condition	Impaired Vision[2]	Severe Visual Impairment[3]	Legal Blindness[4]
Retinal Disorders (Prenatal)	76	72	30
Retinal Disorders (Diabetic)	138	70	22
Retinal Disorders (Other)	601	250	66
Retrolental Fibroplasia	19	19	10
Myopia	715	36	14
Other Less Severe, Imperfectly Correctible Refractive Errors	1,662	0	0
Uveitis	285	67	23
Corneal or Scleral Disorders	294	67	22
Cataract (Prenatal)	41	34	16
Cataract (Other)	1,670	183	48
Glaucoma	1,070	207	56
Optic Nerve Disease	121	107	41
Multiple Conditions	90	90	23
Other Conditions	3,656	103	45
Unknown	221	179	53
Total	10,659	1,483	468

[1]Westat, Inc: *Summary and Critique of Available Data on the Prevalence and Economic and Social Costs of Visual Disorders and Disabilities*, Rockville, MD, 16 February 1976.

[2]Impaired Vision is defined as any reported trouble seeing, with one or both eyes, even when wearing glasses. The numbers here include those in the following two categories.

[3]Severe Visual Impairment is defined as an inability to read ordinary newsprint with glasses using both eyes (six years of age or older), no useful vision in either eye, or blindness in both eyes (any age).

[4]Legal Blindness is defined as visual acuity for distant vision of 20/200 or less in the better eye, with best correction, or widest diameter of visual field subtending an angle less than 20 degrees.

Table 3

Relative Prevalence of Disability for Visual Disorders by NEI Program[1] United States, 1972

NEI Program	Impaired Vision	Severe Visual Impairment	Legal Blindness
Retinal and Choroidal Diseases[2]	27	46	47
Corneal Diseases[3]	4	6	6
Cataract[4]	26	19	18
Glaucoma[5]	16	19	16
Sensory and Motor Disorders of Vision[6]	27	10	12
Total	100%	100%	100%

[1]Based on data in Table 2, excludes Other Conditions, includes prorated share of Multiple Conditions & Unknown.

[2]Includes statistics on Retinal Disorders (Prenatal, Diabetic, and Other), Retrolental Fibroplasia, Myopia, and Uveitis.

[3]Includes statistics on Corneal or Scleral Disorders. Because the great majority of corneal disorders are acute conditions, their impact is not fairly represented by prevalence data. Over 2 million cases of corneal disorders occur each year in the United States, and over 1.7 million injuries to the cornea or external eye are also recorded annually. These account for 62 percent of the total incidence of all acute and chronic disorders, diseases, and injuries to the eye. (See the report of the *Corneal Diseases* Panel for additional data.)

[4]Includes statistics on Cataract (Prenatal and Other).

[5]Includes statistics on Glaucoma.

[6]Includes statistics on Other Less Severe, Imperfectly Correctible Refractive Errors and Optic Nerve Disease.

- 6.2 million people in the United States aged 4 to 74 have visual acuity of 20/50 or worse in their better eye, a level below that required for obtaining a driver's license in most states. Of those aged 65 to 74, about one in seven have such restricted vision.[3]
- Approximately 800,000 people are discharged from hospitals each year with an eye disease or condition as a recorded diagnosis.[4]

Other data on the extent of the problem of eye disorders are provided in the reports of the program planning Panels, and for a detailed summary of the Westat report, the reader is referred to the Council's 1976 interim report.[5] However, it should be apparent from this brief review that disorders of the eye and visual system constitute a health problem of major proportions in the United States. Although they are seldom fatal, such disorders may cause a lifetime of hardship and financial burden. They interfere with the normal social development of thousands of children, seriously restrict the daily activities of millions of adults, and rob a large portion of our elderly of the rewards of their retirement years.

Although these data are impressive, they have significant limitations and must to a great extent be qualified according to the definitions employed, data gathering methods used, experience of those collecting the information, and a number of other variables.

Except for the data on legal blindness, which were extrapolated from information collected by the Model Reporting Area for Blindness Statistics, supported until 1972 by the National Eye Institute, these statistics come from nationwide surveys and studies which collected information on a broad range of health and disease problems. Detailed information on eye diseases cannot be obtained from these sources, and for some significant genetic, developmental, and degenerative disorders such as retinitis pigmentosa, amblyopia, and macular disease, specific prevalence data are not available at all.

Such studies also provide very little information on early eye pathology, because the data are restricted to conditions causing impaired vision. For example, although the largest estimate of the prevalence of glaucoma in Table 2 is slightly over 1 million, the National Society for the Prevention of Blindness estimates that 2 million Americans over age 45 may have this disorder; many of these cases are considered as yet undiagnosed or are being successfully controlled with medical treatment.[6] Because knowledge of the total population with this disease is important when evaluating the need for research on new or improved treatment methods or on possible cure or prevention of this disorder, it would be desirable to gain additional data on glaucoma prevalence.

The Council appreciates the difficulty and potentially great cost of obtaining better and more definitive data on the incidence, prevalence, and economic burden of eye disorders and blindness. However, because of the importance of such information to program planning and for evaluating the impact of research advances, we believe that additional efforts to obtain such data are justified. We concur with the

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[3]National Center for Health Statistics: Monocular Visual Acuity of Persons 4-74 Years, United States, 1971-1972. *Vital and Health Statistics*, Series 11, Number 201, US DHEW Publ No (HRA) 77-1646, Washington, DC, 1977.

[4]National Center for Health Statistics: Inpatient Utilizationof Short-Stay Hospitals by Diagnosis, United States, 1972. *Vital and Health Statistics*, Series 13, Number 20, US DHEW Publ No (HRA) 76-1771, Washington, DC, 1975.

[5]*Support for Vision Research: Interim Report of the National Advisory Eye Council.* US DHEW Publ No (NIH) 76-1098, 1976.

[6]National Society for the Prevention of Blindness: *A Guide for Community Control of Glaucoma.* New York, 1978.

National Eye Institute's decision to terminate the Model Reporting Area for Blindness Statistics because the quality of the data obtained was uncertain; the degree of underregistration, particularly in certain socioeconomic groups, was unknown; no significant trends were apparent in the eight years that the project was underway; and because of the sizeable staff resources required to maintain this project. However, the NEI should at least explore the possibility of a pilot project, perhaps conducted under contract, to obtain blindness data from a well-defined, representative sample population, emphasizing the need for quality in data collection and verification and including a built-in mechanism for periodic assessment and evaluation.

The Council is pleased that the first of a series of reports resulting from NEI collaboration with the National Center for Health Statistics in the 1971-1972 Health and Nutrition Examination Survey has recently been published[3] and that subsequent reports will be forthcoming in the future. We look forward to reviewing these reports, which are based on data from ophthalmological examinations of a representative sample of the U.S. population.

A further contribution to the field has been the Framingham Eye Study, conducted under NEI contract. Initial findings from this project, in which participants in the well-known Framingham Heart Study received detailed ophthalmic examinations, on the prevalence of four leading causes of blindness — senile cataract, diabetic retinopathy, senile macular degeneration, and open-angle glaucoma — have recently been reported.[7] A report of an association of ophthalmic pathology with some of the variables previously measured in the Framingham Heart Study has also been published.[8] These reports are of great interest, but further analysis of the data is required before definitive conclusions can be reached. However, another important contribution of the Framingham Eye Study has been its efforts to standardize and objectify eye examination techniques and to develop procedures that minimize unconscious bias and variability among examiners. These methods provide a model for the design of other epidemiological studies of eye disorders.

The Council has been informed that other plans by the National Eye Institute to obtain reliable data on the extent of the problem of eye disorders include (a) an assessment of the feasibility of obtaining eye disease incidence data from ongoing nationwide samplings of records of physicians' visits and (b) a pilot project in cooperation with the National Center for Health Statistics to obtain ocular prevalence data from eye examinations on a selected population of individuals who have documented visual acuity problems. The Council wishes to commend the National Eye Institute on its continuing interest in obtaining reliable statistical information on the magnitude of the problem of visual disorders and looks forward to utilizing the results of such studies in its future planning activities.

Program Planning Process

In November 1973, the Director of the National Eye Institute discussed the need for vision research program planning with the National Advisory Eye Council and suggested that the Council provide leadership in this area. Concurring with this suggestion, the Council established a Vision Research Program Planning Subcommittee to conduct an extensive analysis of the NEI's current research program and formulate recommendations for its future development.

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[7]Kahn HA, Leibowitz HM, Ganley JP, Kini MM, Colton T, Nickerson RS, Dawber TR: The Framingham eye study. I. Outline and major prevalence findings. *Am J Epidemiol* 106:17-32, 1977.

[8]Kahn HA, Leibowitz HM, Ganley JP, Kini MM, Colton T, Nickerson RS, Dawber TR: The Framingham eye study. II. Association of opthalmic pathology with single variables previously measured in the Framingham heart study. *Am J Epidemiol* 106:33-41, 1977.

Subcommittee Activities

The result of the Subcommittee's activities was the report, *Vision Research Program Planning*, published in April 1975 and followed by an interim data report, *Support for Vision Research*, in April 1976. During the past two years, a new, expanded Program Planning Subcommittee of the Council whose members are listed in Chapter 8, *Program Planning Participants*, has attempted to respond further to the charge to the original Subcommittee:

- Assess the major scientific needs and opportunities in the various fields of vision research;
- Identify research priorities based on detailed analysis of the current National Eye Institute program as well as vision research funded by other agencies and organizations;
- Advise the Council concerning the best distribution of vision research resources.

As in its first report, with this publication the Subcommittee seeks to encourage additional research in important areas where activity is low, hopes to stimulate research in important areas where currently no work is being performed, and reexamines areas where there is already a considerable amount of research underway to determine if further expansion is warranted in the near future.

In performing these tasks, the Subcommittee kept in mind the following five factors which assert that program planning is essential:

- The continued limitation of resources for vision research;
- The periodic fluctuations in federal biomedical research support and their effect upon the continuity of vision research;
- The desire of the National Eye Institute to be fully accountable to the Administration, Congress, and the American people for the expenditure of research funds;
- The need for a systematic means of determining the appropriate level of federal support for vision research;
- The capability of research planning for encouraging the highest possible rate of advancement in the sciences related to vision.

In formulating planning procedures applicable to the National Eye Institute's program, the Subcommittee applied the following general principles established for the Council's first planning report:

- Research planning procedures must not disrupt the extremely successful ongoing research program of the National Eye Institute;
- Reliance on the research grant as the primary mechanism of research support must be sustained;
- There must be continued dependence on peer review for initial assessment of the scientific merit of proposals for individual research projects;
- Responsive research program planning must be a prospective, continuing process in which all data, reports, and Council recommendations are promptly made available to members of the scientific community and to the general public.

In addition to these general principles, the Subcommittee also adopted the following precepts that are specifically pertinent to research program planning at the National Eye Institute:

- Continue to fund all proposals for research projects which are judged by initial review groups to be of the highest scientific quality;
- Emphasize research that is most relevant to the prevention, diagnosis, and treatment of blinding and disabling disorders of the eye and visual system;
- Stress basic biological and applied clinical research on problems related to the most common causes of blindness and visual disability;
- When research involves laboratory animals, favor the utilization of those species for which both scientific opportunity and technical feasibility permit the greatest amount of generalization to the human condition.

Based on these principles and precepts, the following activities were carried out:

- Assessment of the overall vision research effort in the United States;
- Analysis of the importance of all major diseases and disorders of the eye and visual system;
- Evaluation of recent research accomplishments in the prevention, diagnosis, and treatment of these diseases and disorders;
- Formulation of research program goals and objectives;
- Identification within each research program of needs and possible approaches in areas that deserve increased emphasis;
- Selection from among these of priorities and recommendations for achieving more effective program balance;
- Estimation of the resources required to carry out these recommendations.

Program Planning Panels

These activities were begun in the summer of 1975 when the Council established six program planning Panels, each consisting of experts in various fields of vision research. Panel chairmen for each of the five NEI programs (*Retinal and Choroidal Diseases, Corneal Diseases, Cataract, Glaucoma,* and *Sensory and Motor Disorders of Vision*) and for *Vision Research Training* were appointed by the Council and charged with selecting appropriate Panel members and consultants for the purpose of preparing reports which would include the elements outlined above. A list of Panel chairmen, members, and consultants also appears in Chapter 8.

To facilitate the Panels' work, the Subcommittee developed an outline to be used in preparing these reports. However, it did not insist upon strict adherence to the outline at the expense of the free flow of ideas or the effective presentation of special concerns that the Panels might wish to emphasize. That the six Panel reports ultimately differ somewhat in organization, style, and approach is the result of innate differences in the nature of the NEI programs they cover and the types of research approaches considered. Furthermore, the Council gave considerable latitude to each Panel chairman to write a report in a manner best suited to the subject and to the expression of his Panel's views.

Nevertheless, all the Panel reports generally follow a common format. These reports may be found in their entirety in Volume Two of this plan; abridged versions are presented in this volume in Chapter 5, *Summaries of the Panel Reports.* Each report, with the exception of *Vision Research Training,* begins with a foreword which gives an overview of the program and describes how that Panel went about preparing its report. All reports have an introduction which briefly describes the diseases covered by the program and includes data on their social and economic importance plus a summary of recent advances that have been made in their prevention, diagnosis, and treatment. A statement of program goals and a summary of the Panels' recommendations on research priorities concludes this prefatory section.

The body of each Panel report consists of a detailed analysis of the status of research in each of several subprograms and the requirements for continued research progress. Discussion of each subprogram includes the importance of the problem, review of recent accomplishments, and a statement of research objectives. These are followed by an itemized assessment of current research approaches to the problem, from which a few are selected for priority emphasis.

In selecting these priorities, which are summarized in Chapter 1, *Executive Summary,* of this volume, each Panel has taken into account the public health impact and the scientific importance of a particular visual problem, reviewed the extent and nature of relevant research support by the NEI and other public and private agencies, and judged that additional funding and research effort in a specific area will likely lead to significant progress toward the solution of the problem in a relatively short time. The Panels believed that they should not attempt to rank these priorities further; therefore, they are not necessarily presented in order of importance, but in most cases appear in the order in which they have been discussed in the body of the report. The series of tables presented at the end of each report in Volume Two provides a convenient format for presenting these priorities in terms of numbers of recommended additional projects and for displaying the financial and manpower resources that will be required to carry them out. These tables are not reproduced in this volume, but they are the basis of the Council's proposed five-year budget for the National Eye Institute presented and discussed in Chapter 1.

Council Review and Approval

First drafts of the Panel reports were submitted to the Council's Program Planning Subcommittee in December 1976. At a subsequent meeting with the Panel chairmen, the Subcommittee members made several recommendations for revisions of the reports. These were referred to the full Panel membership for consideration. Over the next several months, numerous exchanges, both formal and informal, took place among Panel chairmen, members, consultants, and the Subcommittee. The ultimate result of this interchange was new drafts of the Panel reports that were mutually acceptable to the Panel and Subcommittee members.

These revised drafts were submitted by the Subcommittee to the Council in advance of a special Council meeting that was held April 12, 1977, to discuss the new planning report. At this meeting, to which the Panel chairmen were invited, the Council gave tentative approval to the draft reports pending incorporation of further changes which were agreed to at that time by the Panel chairmen. The Council requested that, after these changes were made, the National Eye Institute proceed with publishing the reports as the second volume of the Council's new plan. The Council further decided that summaries of these Panel reports should be printed in Volume One of the plan along with its own overview of the current status and future development of the NEI program. A third volume was to include the extensive data

on support for vision research in the United States that had been collected by the National Eye Institute staff for use by the Panels as background for their deliberations.

The Council believes that the steps taken at several stages in the planning process to achieve consensus, first among Panel members, and then among the Panels, the Program Planning Subcommittee, and the full Council, will facilitate the realization of the recommendations contained in this plan. Through such interaction, a unified expression of the views of the Council and its consultants has been achieved. This should enhance the credibility of this document to both the scientific community and the public at large.

Progress Toward Achieving Program Goals

In its 1975 planning report, the National Advisory Eye Council accorded special attention to 24 research topics which, in its judgment and that of its consultants, not only were highly important to the prevention, diagnosis, and treatment of visual system disorders but also were likely to be productive lines of inquiry. While it is clearly too soon to draw any definitive conclusions about the substantive impact of these recommendations upon the course of vision research and the quality of eye care, preliminary data on award rates for research grants in the wake of the Council's report are encouraging.

The 24 areas of special need and opportunity for vision research identified in the first Council report, organized by program, are shown in Table 4. Table 5 presents the number of grant awards in each category for fiscal years 1974, 1975, and 1976 — the period immediately preceding and following publication of the report. Also indicated in Table 5 is the total number of grant awards in each program.

Several observations about this data seem pertinent.

- Overall, the National Eye Institute's current support of vision research clearly reflects the recommendations in the Council's first report. Of the net increase of 219 grant awards between FY 1974 and FY 1976 for all programs, 112 (51 percent) were in the 24 areas identified for special emphasis.

- In 9 of the 24 special emphasis areas, a substantial increase in the level of activity occurred between FY 1974 and FY 1976, i.e. increases of from 59 percent to 367 percent. Five of these significant increases were in the *Retinal and Choroidal Diseases* program (numbers 1, 2, 3, 6, and 8), one was in the *Corneal Diseases* program, (number 1), one was in the *Cataract* program (number 2), and two were in the *Sensory and Motor Disorders of Vision* program (numbers 1 and 5). For these 9 areas, it is apparent that the report both reflected and reinforced emerging trends in vision research.

- The closest correspondence between the Council's recommendations and the subsequent pattern of awards are found in the *Retinal and Choroidal Diseases* and *Sensory and Motor Disorders of Vision* programs. For *Retinal and Choroidal Diseases*, there was a notable increase in the number of NEI-sponsored projects in six of the eight areas identified; and of the net increase of 105 grant awards for the entire program between FY 1974 and FY 1976, 52 (49.5 percent) were in the areas of special emphasis. Similarly, for *Sensory and Motor Disorders of Vision*, there was a major increase in the number of NEI-sponsored projects in three of the four areas identified; of the net increase of 54 grant awards for the entire program between FY 1974 and FY 1976, 38 (70 percent) were in the special emphasis areas.

- By contrast, the *Glaucoma* program had the least correspondence between the Council's recommendations and the subsequent pattern of awards. There was no significant change in the level of research activity in any of the special emphasis areas; of the net increase of 17 grant awards for the entire program between FY 1974 and FY 1976, only 2 (12 percent) were in the identified high priority areas.

There are several possible reasons why some of the recommendations in the Council's 1975 report are not reflected in the grant award rates to date. The obstacles to progress in certain areas may have been underestimated, e.g. the difficulty of identifying and gaining ready access to good animal models of human visual disorders or the absence of a critical mass of investigators with the special expertise needed to exploit a particular research opportunity. Other recommendations may not be convincing to investigators, e.g. the majority of the vision research community may disagree with the Council's assessment of either the importance of the

Table 4

Major Vision Research Needs and Opportunities from the 1975 National Advisory Eye Council Report

Retinal and Choroidal Diseases

1. Pigment epithelium research merits increased emphasis because of the basic relationship of the pigment epithelium to retinal function and the recent development of new techniques for basic science and clinical investigation.
2. Retinal organization and information processing are deserving of increased study, particularly in primates with systems likely to be comparable to those of man.
3. Retinal pigmentary dystrophies and retinal storage diseases, encompassing a detailed study of retinal biochemistry, warrant greater research attention.
4. Retinal and choroidal circulation requires increased study because of its relevance to diabetic retinopathy, macular degeneration, and other major disease entities, and because of the availability of new research techniques.
5. The development of practicable animal models for inflammatory diseases of the choroid and retina should be emphasized.
6. Clinicopathologic correlations between disease pictures observed in the retina and choroid and the histologic, biochemical, and physiologic manifestations of those diseases should be further developed, particularly for diseases in which, as yet, no adequate histopathologic documentation of the entity exists.
7. Clinical research related to retinal and choroidal diseases is recommended, with emphasis on research protocols, precise measurement of clinical parameters, and the selective use of controlled, randomized clinical trials. Clinical investigations are essential for evaluating existing therapeutic regimes and appraising the efficacy of new methods of therapy.
8. Tumors of the retina and choroid warrant increased research in view of the genetic aspects of retinoblastoma, the discovery of intraocular enzyme abnormalities in eyes with retinoblastoma, and the emerging role of immunologic procedures for tumor diagnosis and the assessment of prognosis.

Corneal Diseases

1. Tissue culture, with appropriate biomedical analysis of abnormal human corneal tissue removed at the time of corneal transplantation should be stressed.
2. Immunologists should be encouraged to become involved in corneal research and to address major problems related to disease and graft systems.
3. Additional controlled clinical trials of new antiviral drugs useful in treating herpes simplex and other important infective diseases are needed.
4. The possible role of viruses in the causation of neoplasms affecting the cornea and conjunctiva warrants emphasis.

research problem or its readiness for emphasis, or both. Still other recommendations may be stated too broadly or too narrowly to make meaningful tracking of the course of vision research in these areas possible. There are, no doubt, other explanations, but the apparent lack of progress in some areas may also simply point to the need for a greater effort to implement the Council's recommendations, as discussed in the preceding chapter.

Whatever the reason for the seeming lack of progress in certain areas, the Council has attempted in the present report to reaffirm and clarify those of its previous recommendations for which there has been no significant increase in the number of new grants to date (myopia research and clinical trials of alternative techniques for optical rehabilitation after cataract surgery are two examples). And, in concert with the staff of the National Eye Institute, the Council will continue to accumulate and analyze data on the correspondence between planning recommendations and research trends and use the resultant findings to improve the methodology of research program planning.

Cataract

1. Investigations of the biochemical and biophysical processes operative in the maintenance of normal lens hydration, particularly in primates and human beings, are important and should be stimulated. These studies provide the background for studying how aberrations in these mechanisms lead to lens opacification.
2. The study of protein changes in the lens and the role of protein aggregation in the development of cataracts requires increased emphasis.
3. The search for new animal models for studying congenital cataracts and for investigating the degenerative processes associated with aging and cataract production should be encouraged.
4. Attention should be given to the organization of controlled, randomized clinical trials to evaluate alternate techniques for surgical management of cataract and to assess alternate methods for optical rehabilitation.

Glaucoma

1. Studies of the mechanism of pressure-induced visual function damage in the primate and in man should be emphasized.
2. Investigations on the mechanisms of aqueous production and outflow in primates and man deserve encouragement.
3. Controlled, randomized clinical trials of medical and surgical therapy for open-angle glaucoma should be conducted.
4. Research designed to predict, with increasing accuracy, the risk of closed-angle glaucoma warrants increased support.

Sensory and Motor Disorders of Vision

1. Further studies of strabismus and amblyopia, especially in primates, should be undertaken and other useful experimental models of these disorders developed.
2. Physiologic, neurochemical, and pharmacologic studies of oculomotor control, particularly in monkeys, warrant increased emphasis.
3. There is particular need for research leading to the prevention of degenerative, high myopia and to the prevention of the changes associated with this condition that may endanger sight.
4. Research on neural mechanisms in the sensory system, and the correlation of these mechanisms with psychophysical functions and the processes of vision, should be directed toward maximization of residual vision function following disease of the visual pathways.

Table 5

National Eye Institute Awards According to National Advisory Eye Council 1975 Research Priorities

	FY 1974	FY 1975	FY 1976
All Programs			
Total Awards in Priority Areas	192	231	304
Total Awards in All Programs	424	495	643
Retinal and Choroidal Diseases			
1. Pigment epithelium	6	11	14
2. Retinal organization/information processing in primates	10	15	16
3. Pigmentary dystrophy and retinal storage diseases	34	36	54
4. Retinal and choroidal circulation	17	15	23
5. Animal models for inflammatory diseases	9	8	8
6. Clinicopathologic correlations	9	10	16
7. Clinical research/trials	14	11	15
8. Tumors	4	7	9
Total Awards in Priority Areas	103	113	155
Total Awards in Program	145	176	250
Corneal Diseases			
1. Tissue culture of abnormal human tissue	4	7	7
2. Immunology	14	15	17
3. New antiviral drugs	3	3	3
4. Viruses in corneal neoplasms	0	0	0
Total Awards in Priority Areas	21	25	27
Total Awards in Program	70	79	89
Cataract			
1. Normal lens hydration	0	1	1
2. Lens protein changes	5	9	17
3. Animal models	6	6	7
4. Clinical trials of surgery and optical rehabilitation	0	0	0
Total Awards in Priority Areas	11	16	25
Total Awards in Program	46	52	70
Glaucoma			
1. Mechanism of pressure-induced damage in primates and man	7	6	6
2. Mechanism of aqueous production and outflow	19	21	20
3. Clinical trials of open-angle glaucoma therapy	3	3	5
4. Predicting the risk of closed-angle glaucoma	0	0	0
Total Awards in Priority Areas	29	30	31
Total Awards in Program	43	50	61
Sensory and Motor Disorders of Vision			
1. Strabismus and amblyopia in primates	3	7	14
2. Oculomotor control in monkeys	16	20	22
3. Prevention of degenerative high myopia	0	0	1
4. Correlation of neural mechanisms with psychophysical functions	9	20	29
Total Awards in Priority Areas	28	47	66
Total Awards in Program	120	138	174

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Program Data Summary

IN THIS CHAPTER, statistical data used by the Council and its consultants in preparing this report are summarized. Tables 1 through 3 provide information on support for vision research by organizations in the United States during FY 1976. The National Eye Institute, other Institutes of the National Institutes of Health, other components of the Department of Health, Education, and Welfare, as well as other agencies of the federal government are included. There is also a representative list of the support provided by major national private, philanthropic, and voluntary health agencies. Excluded from this compilation because of incomplete or unavailable data are research projects supported by local and state governments, foreign governments, universities, corporations, and the private resources of individual investigators.

Historical data on National Eye Institute funding and obligations are developed in Tables 4 through 9.

Table 1 summarizes the detailed lists of vision research projects supported during FY 1976 by organizations in the United States that are included in Volume Three of this report, *Support for Vision Research*. Abstracts for all projects appearing in that volume were carefully reviewed to determine the relevance of the project to the mission of the National Eye Institute. Only those projects whose primary objective or concern is to learn more about the eye and the visual process in health and disease were included in the totals which appear in this Table.

In fiscal year 1976, over $72 million was spent for vision research by federal government and national not-for-profit organizations in the United States. These funds were provided by the National Eye Institute, other Institutes of NIH and other DHEW agencies, other organizations within the federal government, and by national private, philanthropic, and voluntary health organizations. Of these, the National Eye Institute was the largest single source of vision research support, accounting for 69 percent of the total funds.

Excluded from these totals are approximately $28 million in projects listed in Volume Three as being indirectly relevant to the mission and program of the National Eye Institute. These include projects in which the visual system plays some part but whose chief purpose is something other than learning more about the eye and vision in health and disease. Also excluded are studies which do not involve the eye but which may have some bearing on normal and abnormal ocular structure and function. The distinction made between projects of direct or indirect relevance to the National Eye Institute's program is discussed further in the Introduction to Volume Three.

Table 1

Summary of Vision Research Funding
FY 1976

	Amount of Funding	Percent of Funds
Federal Government		
National Eye Institute	$50,212,000	69
National Institutes of Health (Exclusive of NEI)	8,568,156	12
Department of Health, Education, and Welfare (Exclusive of NIH)	4,079,217	6
Other Federal Support	7,541,532	10
National Private, Philanthropic, and Voluntary Health Organizations	2,176,924	3
Total	$72,577,829	100

Table 2 breaks down the totals in Table 1 according to federal agencies and national private, philanthropic, and voluntary health organizations. That components of NIH other than the National Eye Institute provide support for vision research demonstrates the variety of disease and scientific problems with which this discipline is concerned. In some instances, this support is for projects that include the eye among a number of organ systems in which a particular disease is being studied. In such cases, an attempt has been made to identify that portion of funding limited to the eye alone, although this is frequently difficult to do. The fact that an Institute other that the National Eye Institute is supporting any given project indicates either that the primary focus of the research is oriented to the mission of that Institute (e.g. a project investigating the role of systemic hypertension in diabetic retinopathy may be supported by the National Heart, Lung, and Blood Institute) or that NEI funds were not available to support the project at the time it was approved but another Institute, whose mission also encompassed the project, was interested in and able to fund it.

Vision research supported by other DHEW programs and by other federal agencies is also closely related to the overall mission of the funding organization. Examples are a study of infectious keratitis in cattle supported by the Department of Agriculture and investigations by the Department of Defense of protective measures for combat-related laser irradiation of the eye. Vision research supported by the National Science Foundation is primarily concerned with basic neural mechanisms; vision research underway in Veterans Administration hospitals is concerned with the problems often encountered in patients seen in these institutions. In a number of instances, the Veterans Administration research projects are conducted in relationship to other projects supported by the NEI and frequently involve the same principal investigator.

Table 2
Sources of Vision Research Funding FY 1976

Department of Health, Education, and Welfare	
National Institutes of Health	
National Eye Institute	$50,212,000
National Cancer Institute	1,037,210
National Heart, Lung, and Blood Institute	850,151
National Institute of Arthritis, Metabolism, and Digestive Diseases	427,481
National Institute of Allergy and Infectious Diseases	123,538
National Institute of Communicative Disorders	3,733,447
National Institute of Child Health and Human Development	1,111,806
National Institute of Dental Research	24,414
National Institute of General Medical Sciences	565,896
National Institute on Aging	25,452
Division of Research Resources	668,761
Subtotal: National Institutes of Health (Exclusive of NEI)	**$ 8,568,156**
Food and Drug Administration	323,478
Health Resources Administration	50,000
National Institute for Occupational Safety and Health	59,549
National Institute of Education	160,000
Alcohol, Drug Abuse, and Mental Health Administration	
National Institute of Mental Health	2,657,570
National Institute on Alcohol Abuse and Alcoholism	317,861
National Institute on Drug Abuse	78,860
Social and Rehabilitation Service	431,899
Subtotal: Department of Health, Education, and Welfare (Exclusive of NIH)	**$ 4,079,217**
Other Federal Support	
Consumer Product Safety Commission	47,500
Department of Agriculture	358,776
Department of Commerce	75,000
Department of Defense	226,000*
Air Force	1,240,254
Armed Forces Institute of Pathology	81,631
Army	1,245,384
Navy	697,453
Energy Research and Development Administration	42,934
National Aeronautics and Space Administration	56,000
National Science Foundation	2,818,400
Veterans Administration	652,200
Subtotal: Other Federal Support	**$ 7,541,532**
National Private, Philanthropic, and Voluntary Health Organizations	
American Association of Workers for the Blind	17,000
American Cancer Society	171,593
Cleveland Foundation	12,708
Council for Tobacco Research, U.S.A.	24,815
Charles A. Dana Foundation	106,350
Estelle Doheny Eye Foundation	177,046
Eye Bank for Sight Restoration	74,000
Fight for Sight, Inc.	201,680
Max C. Fleischmann Foundation	298,000
John A. Hartford Foundation	18,388
Charles E. Hood Foundation	11,532
Juvenile Diabetes Foundation	163,651
The Moody Foundation	14,000
National Eye Research Foundation	10,000
National Retinitis Pigmentosa Foundation	263,816
National Society for the Prevention of Blindness	40,500
Research Corporation, Cleveland	8,145
Research to Prevent Blindness, Inc.**	310,000
Helena Rubinstein Foundation	25,000
William E. and Bertha F. Schrafft Foundation	12,000
Seeing Eye, Inc.	50,000
Sloan Kettering Institute	50,000
Spencer Foundation	106,700
Matilda Ziegler Foundation	10,000
Subtotal: National Private, Philanthropic, and Voluntary Health Organizations	**$ 2,176,924**
Total	**$ 72,577,824**

* Two projects were funded at the Department level.

** This does not include $5,466,000 raised for building eye research centers during 1976 through RPB's laboratory construction program.

It must be stressed that the contribution made by private, philanthropic, and voluntary health organizations to the national vision research effort cannot be measured by dollars alone, for the importance of these groups extends far beyond their financial outlays. Time and again such organizations have provided support and encouragement to promising young investigators. Often, they have provided funding for facilities construction, equipment, or other vital research resources that could not be obtained elsewhere. These groups are also frequently able to act quickly to provide timely funding for the development of innovative techniques or for exploiting unusual opportunities that may otherwise have been lost in the course of the longer time period necessarily required for review of government research grant applications. Finally, such organizations perform an important function in focusing national attention on important unmet needs and in dramatizing the importance of research to the improvement of human health.

For these reasons, regardless of the future growth of government support for vision research, the Council believes it is essential to the attainment of the goals and objectives outlined in this plan that the private organizations in this field continue to flourish and grow. For, in addition to their financial support, they provide a spirit of dedication and a type of enthusiasm that inspires all of those who work to conquer blindness and visual disability.

For detailed information on the projects supported by these agencies, see Volume Three, *Support for Vision Research.*

Table 3 categorizes national support for vision research, whether by the federal government or private, philanthropic, and voluntary agencies, according to the five research programs of the National Eye Institute. A sixth category has been added for vision research funds not designated for a specific purpose.

Table 3
United States Vision Research Support
by National Eye Institute Program
FY 1976

	Retinal and Choroidal Diseases	Corneal Diseases	Cataract	Glaucoma	Sensory and Motor Disorders of Vision	Multiprogram	Total
Federal Government							
National Eye Institute	$16,215,000	$ 6,890,000	$ 4,282,000	$ 6,561,000	$ 8,524,000	$ 7,740,000*	$50,212,000
National Institutes of Health (Exclusive of NEI)	3,079,396	397,043	271,600	196,794	4,623,323	—	8,568,156
Department of Health, Education, and Welfare (Exclusive of NIH)	278,898	67,000	32,549	72,708	3,628,062	—	4,079,217
Other Federal Support	1,526,912	1,022,400	510,544	56,000	4,425,676	—	7,541,532
National Private, Philanthropic, and Voluntary Health Organizations	921,119	276,132	50,750	37,593	574,980	316,350	2,176,924
Total	$22,021,325	$ 8,652,575	$ 5,147,443	$ 6,924,095	$21,776,041	$ 8,056,350	$72,577,829

* Direct Operations.

Table 4

National Eye Institute Appropriation History
FY 1970-1978

Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation	Appropriation in Constant Dollars*
1970	$23,685,000	$23,685,000	$25,000,000	$24,342,500	$(24,342,500)
1971	25,686,000	30,986,000	30,986,000	30,032,000	(28,439,000)
1972	32,639,000	36,022,000	40,187,000	37,132,500	(33,574,000)
1973	37,384,000	38,562,000	45,000,000	38,562,000	(33,387,000)
1974	32,092,000	36,631,000	46,631,000	41,166,000	(33,333,000)
1975	39,947,000	38,878,000	50,000,000	44,133,000	(32,285,000)
1976	39,201,000	42,608,000	50,000,000	50,212,000	(31,102,000)
1977	46,950,000	56,270,000	70,000,000	64,000,000	(40,868,000)
1978	64,981,000	—	—	—	—

* The following price deflators were developed by the Division of Program Analysis, NIH, to compute constant dollars:

1970—100.0 1973—115.5 1976—146.5
1971—105.6 1974—123.5 1977—156.6
1972—110.6 1975—136.7

The National Eye Institute's appropriation history is presented in Table 4. The NEI appropriation has increased by 163 percent during the past eight years, but in terms of constant (1970) dollars, NEI funding has grown a modest 68 percent.

The National Eye Institute's funding history by budget activity displayed in Table 5 indicates that total extramural research funding has more than doubled since FY 1971 and has kept steady at about 85 percent of the total NEI budget for each of those years. Investigator-initiated research project grants have accounted for an average 80 percent of extramural support. Research contracts have averaged 5 percent of the total NEI budget, intramural laboratory and clinical research has remained at about 10 percent of the total, and research management and program services has stayed level at 3 percent of the total budget.

Table 6 is an analysis of the NEI budget by its program components. Comparable data for fiscal years before 1974 are not available because the NEI budget was not prepared in this form until that year. These programs were established by grouping NEI's existing grants according to their relevance to one of five major types of related visual disorders. Allocations for each succeeding year are based upon prior year commitments and estimates of the number and amount of new and renewal grant applications that will be received in each program category. In recent years, this process has been augmented by considerations of major research needs and opportunities in each program as documented in this report. The National Eye Institute's own budget recommendations are, of course, subject to modification at each of several successively higher levels of government review, with the ultimate amounts determined each year by the Congress and agreed to by the President.

Under program budgeting, all research grant applications compete with one another during the initial review for scientific merit, but funding restrictions within programs determine the number of new and renewal grant applications which are actually paid. Under certain circumstances, some reprogramming by the National Eye Institute is allowed during the course of the fiscal year if such a

step is considered necessary to ensure the continued quality of the overall research effort. Any reprogramming must be approved at levels higher than the National Eye Institute, including NIH, the Public Health Service, DHEW, and/or the Congress.

Program budgeting not only facilitates NEI's day-to-day management but provides a rational basis for program planning and helps assure accountability to the public in addressing major national problems related to blindness and visual disability.

The programs listed in this Table include all research grant, fellowship, and contract funds. The *Retinal and Choroidal Diseases* program has averaged about 40 percent of the extramural budget. The *Corneal Diseases* and *Glaucoma* programs have each averaged approximately 15 percent; *Cataract*, 10 percent; and *Sensory and Motor Disorders of Vision* has averaged about 20 percent.

Table 5

NEI Funding History by Budget Activity Obligations FY 1971—1977 (Dollars in Thousands)

	FY 1971 Funds	FY 1972 Funds	FY 1973 Funds	FY 1974 Funds	FY 1975 Funds	FY 1976 Funds	Transition Quarter FY 1976 Funds	FY 1977 Funds
Extramural Research*								
Research Grants	19,203	23,399	23,849	27,784	29,635	35,503	6,349	46,024
Fellowships	1,676	1,676	1,802	1,652	2,653	2,653	416	3,453
Training Grants	2,998	2,998	3,398	2,903	1,994	1,994	—	1,187
Research Contracts	1,332	2,122	2,122	2,122	2,322	2,322	844	3,522
Total Extramural	25,209	30,195	31,171	34,461	36,604	42,472	7,609	54,186
Direct Operations								
Intramural Laboratory and Clinical Research	1,570	1,935.5	2,041	2,325	2,683	2,535	590	3,380
NIH Management Fund**	319	1,417	1,506	1,998	2,217	2,558	667	3,231
Subtotal	1,889	3,352.5	3,547	4,323	4,900	5,093	1,257	6,611
Biometry, Epidemiology and Field Studies	331	386	421	414	410	339	100	476
NIH Management Fund**	16	68	46	61	77	72	4	11
Subtotal	347	454	467	475	487	411	104	487
Research Management and Program Services	789	1,205	1,200	1,360	1,545	1,652	384	2,032
NIH Management Fund***	247	341	424	547	597	584	165	684
Subtotal	1,036	1,546	1,624	1,907	2,142	2,236	549	2,716
Total Direct Operations	3,272	5,352.5	5,638	6,705	7,529	7,740	1,910	9,814
Grand Total	28,481	35,547.5	36,809	41,166	44,133	50,212	9,519	64,000

* This excludes funds contained in appropriation bill for NIH General Research Support Grants in FY 1971, 1972, and 1973. These amounts were $1,551,000, $1,585,000, and $1,753,000, respectively.

** These portions of the NIH Management Fund are assessments based on the central NIH services provided to NIH direct research activities conducted at the NIH campus in Bethesda, Maryland. These services include operation of the NIH Clinical Center, engineering services, utilities, computer services, and other research services.

*** This portion of the NIH Management Fund is an assessment based on central NIH services provided for the general management and program direction activities of the NEI. These services include central NIH receipt and review of research grants, centralized NIH financial management and other administrative services.

Table 6

NEI Obligations by Program
FY 1974— 1977
(Dollars in Thousands)

	FY 1974 Funds	FY 1975 Funds	FY 1976 Funds	Transition Quarter FY 1976 Funds	FY 1977 Funds
Extramural Programs					
Retinal and Choroidal Diseases	12,402	14,092	16,215	3,515	23,125
Corneal Diseases	6,024	6,596	6,890	922	7,586
Cataract	3,243	3,445	4,282	543	5,524
Glaucoma	5,290	5,012	6,561	774	7,692
Sensory and Motor Disorders of Vision	7,502	7,459	8,524	1,855	10,259
Total Extramural	34,461	36,604	42,472	7,609	54,186
Direct Operations					
Intramural Laboratory and Clinical Research	2,325	2,683	2,535	590	3,380
NIH Management Fund*	1,998	2,217	2,558	667	3,231
Subtotal	4,323	4,900	5,093	1,257	6,611
Biometry, Epidemiology and Field Studies	414	410	339	100	476
NIH Management Fund**	61	77	72	4	11
Subtotal	475	487	411	104	487
Research and Management Program Services	1,360	1,545	1,652	384	2,032
NIH Management Fund**	547	597	584	165	684
Subtotal	1,907	2,142	2,236	549	2,716
Total Direct Operations	6,705	7,529	7,740	1,910	9,814
Grand Total	41,166	44,133	50,212	9,519	64,000

* These portions of the NIH Management Fund are assessments based on the central NIH services provided to the NEI direct research activities conducted at the NIH campus in Bethesda, Maryland. These services include operation of the NIH Clinical Center, engineering services, utilities, computer services, and other research support services.

** This portion of the NIH Management Fund is an assessment based on central NIH services provided for the general management and program direction activities of the NEI. These services include central NIH receipt and review of research grants, centralized NIH financial management, procurement, personnel management, grant and contract management, and other administrative services.

In Table 7, variations from year to year in the percent of research grant applications funded are related both to the number of applications received and the amount of funds available in any given year. The number of grant applications received by the National Eye Institute has increased 154 percent over the six-year period FY 1971 to 1976. Total funds available for research grants during this time have increased by 240 percent, but because of prior commitments, the percent available in any year to fund new and renewal grants may vary considerably. For example, in FY 1977, 65 percent of the total appropriation was already committed to noncompeting continuations of grants activated in preceding years. This left $16 million, one-fourth of the appropriation, to fund all approved renewal and new grant applications for that year.

The number of individual, investigator-initiated research project grants supported by the NEI for each fiscal year since 1970 is presented in Table 8. The number of grants supported by the NEI over this period has grown by 96 percent.

Table 7

National Eye Institute Competing Research Grant Applications History: Reviewed, Approved, and Percent Funded FY 1971—1977

Year	Received and Reviewed	Recommended for Approval After Scientific Review	Approved and Funded	Recommended for Approval But Not Funded	Disapproved	Percent Funded of All Applications Reviewed	Percent Funded of All Applications Approved
1971	227	183	119	64	44	52	65
1972	332	260	139	121	62	43	53
1973	391	319	154*	165	72	40	48
1974	382	335	175	160	47	46	52
1975	318	274	200	74	44	63	73
1976	349	297	199	98	52	57	67
1977	515	428	238	190	87	46	56

* Includes projects supported by impounded funds released in FY 1974 (15 months).

Table 8

Number of Individual Research Project Grants Supported by the National Eye Institute FY 1970-1977

Year	Number of Projects
1970	353
1971	411
1972	421
1973	405
1974	444
1975	511
1976	579
1977	691

Table 9 presents a list of all institutions receiving $500,000 or more from the NEI in total institutional support, including basic and clinical departments, during FY 1976. This list includes many of the major American centers of vision research and eye care; however, some of these institutions have several components—departments of ophthalmology, related medical departments, schools of optometry, or basic science departments—each of which may receive NEI funds. In every case, these funds support the projects of individual investigators. In reviewing these figures, it is important to keep in mind that they include both direct and indirect (overhead) costs. Grantees usually deal in terms of direct costs for their individual projects; indirect costs are paid to the institution.

Table 9
Institutions Receiving $500,000 or More Funding from NEI
FY 1976*

Name of Institution	Research Grants	Training Awards	Research Contracts	Total
Columbia University	$1,732,338	$150,328	0	$1,882,666
Johns Hopkins University	1,498,192	124,609	164,858	1,787,659
University of California, San Francisco	1,515,233	119,116	114,801	1,749,150
Eye Research Institute of Retina Foundation, Boston	1,426,070	77,509	0	1,503,579
University of California, Los Angeles	1,123,079	140,263	95,617	1,358,959
Washington University	1,195,464	144,443	0	1,339,907
Yale University	1,009,585	131,364	0	1,140,949
University of Wisconsin, Madison	681,902	68,863	365,318	1,116,083
University of Washington	746,427	215,381	82,055	1,043,863
Harvard University	867,464	165,382	0	1,032,846
University of Florida	935,507	88,341	0	1,023,848
New York University	682,310	168,384	0	850,694
University of Pennsylvania	500,378	282,016	0	782,394
Stanford University	658,602	114,755	0	773,357
Massachusetts Institute of Technology	562,588	103,963	0	666,551
University of Miami	462,008	127,307	63,895	653,210
Boston University	579,157	68,300	0	647,457
University of California, Berkeley	508,138	122,947	0	631,085
Institutes of Medical Sciences, San Francisco	533,929	42,971	0	576,900
Wills Eye Hospital, Philadelphia	400,192	47,336	91,088	538,616
New England Medical Center Hospital, Boston	439,853	66,999	0	506,852

* Total institutional support including basic and clinical departments.

5

Summaries of the Panel Reports

THIS CHAPTER SUMMARIZES the reports of the six Panels established by the National Advisory Eye Council to assess the needs and opportunities in each of the five National Eye Institute research programs and to make recommendations concerning the future support of vision research training. The complete reports of these Panels constitute Volume Two of *Vision Research—A National Plan.*

The Panels' findings and conclusions provide the basis for the Council's selection of priorities for the next five years of vision research support. These priorities, which are summarized in Chapter 1 of this volume, are related to those presented in detail in Volume Two along with each Panel's specific recommendations concerning the number of projects and the financial and manpower resources that would be required to carry them out.

Each Panel report, with the exception of *Vision Research Training*, begins with a short introduction followed by a discussion of the importance of the disease problem, an overview of the major recent accomplishments in the general field, and a statement of program goals. Next, each of several subprograms is discussed in terms of its importance and relevant accomplishments.

The critical portion of each report is the Panel's assessment of the most important research needs in each subprogram and of the possible approaches to their solution. It is from the latter that priorities were selected for recommendation to the National Advisory Eye Council.

It is evident from these summaries, and especially from the unabridged reports contained in Volume Two, that each Panel considered many more opportunities for research than were included in their final recommendations. This selection process was difficult and necessarily subjective, but because Panel members and consultants were chosen to effect broad representation of basic and applied research in each major field, it is likely that most significant opportunities were considered.

The Council has been fortunate in receiving advice from more than 160 leaders and experts in the complex and dynamic field of modern vision research. (See Chapter 8, *Program Planning Participants*, for the names of all Panel members and consultants.) It is certain that their conclusions, which were based not only upon scientific judgments but upon pragmatic and social considerations as well, have resulted in the determination of priorities which will be credible to the scientific community, have potential for yielding important new knowledge in a relatively short period of time, and be applicable to the solution of important public health problems related to blinding and disabling visual disorders.

Retinal and Choroidal Diseases

Introduction

The retina, the sensory membrane of the eye, is the immediate instrument of vision. It receives visual images transmitted through the cornea, lens, and vitreous humor and converts them to electrical impulses sent to the brain via the optic nerve. Damage to the retina leads to loss of vision and in many cases to blindness.

The vitreous humor is a clear, transparent gel just in front of the retina which fills the entire back of the eye. When, for any reason, the vitreous humor becomes opaque, vision is lost. The choroid is a thin membrane just behind the retina, consisting largely of blood vessels. It provides nourishment to the retina, and damage to the choroid or its malfunction results in deterioration of the retina and loss of vision. Immediately outside the choroid is the white of the eye, a tough collagenous layer called the sclera, which contains the eye's pressure and acts as a support to the choroid and retina. This support must be maintained if the choroid and sclera are to function properly.

Unfortunately, the retina is vulnerable in a remarkable variety of ways. It requires a steady supply of oxygen and nutrients, for which it depends upon two separate blood supplies. The retina must live in a carefully controlled biochemical environment, any derangement of which can lead to a loss of function and to visual impairment. The actual visual receptor cells, the rods and cones, are constantly renewing essential elements of their structure; in order to do so, the rods and cones must live in a cooperative association with another group of cells, the pigment epithelium. Failure of either cell to perform its shared function leads to malfunction of both and results in visual loss.

Diseases involving this system are diverse, and the research program intended to attack them is necessarily complex. It comprises 12 subprograms ranging from hereditary problems to diseases associated with infection, and from damage by toxic agents to visual problems arising from circulatory failure.

Accomplishments

As both an accessible organ and meeting ground for various scientific disciplines, the eye presents unusual opportunities for study. A number of important accomplishments have resulted from research to date:

- Increased understanding of the effects of diabetes on the eye and advances in producing and controlling powerful beams of light have led to development of a helpful treatment for diabetic retinopathy, the leading cause of new blindness among adults.
- Increased understanding of the structure of photoreceptors gives strong promise of eventual control of major degenerative diseases such as retinitis pigmentosa and macular degeneration.
- Research on ocular tumors has produced findings that may be important to the general field of cancer research.
- Study of vascular and circulatory diseases in the retina are clearly applicable to the study of blood vessels elsewhere in the body.
- Research on inflammatory disorders in the eye is providing insight into the body's immunologic processes.

Goals of Retinal and Choroidal Diseases Research

- Enhance understanding of fundamental processes underlying good vision and of their derangement in diseases of the retina and choroid.
- Improve the means to diagnose diseases of the retina and choroid.
- Discover means to prevent retinal and choroidal diseases or to treat these diseases effectively once they occur.

To meet the above goals, adequate, coordinated, and sustained support must be given to both basic and clinical research.

The National Eye Institute's research program in *Retinal and Choroidal Diseases* encompasses specific clinical disorders as well as basic research on development, structure, and function of the eye as related to disease. Also considered are several special areas for future emphasis. The subprograms examined by the Panel are:

- *Problem Areas and Specific Disorders*
  - Developmental and Hereditary Disorders
  - Diabetic Retinopathy and Other Vascular and Circulatory Abnormalities
  - Myopia
  - Tumors
  - Macular Diseases
  - Retinal Detachment
  - Inflammatory Disorders
- *Development, Structure, and Function as Related to Disease*
  - Uveal Tract
  - Vitreous Humor
  - Visual Cells and Pigment Epithelium
  - Retinal Organization and Visual Adaptation
- *Special Areas of Future Interest*
  - Toxic and Environmental Disorders
  - Low Vision
  - Retinal Regeneration and Transplantation
  - Tissue Acquisition and Distribution: Human Donor Eyes and Animal Models

Developmental and Hereditary Disorders

Developmental and hereditary disorders of the retina afflict infants and children and, unfortunately, are relatively common. At present, they are responsible for 33 percent of all blindness among school children in the United States. Both visual disabilities from birth and those which destroy vision in young

life carry with them immense emotional impact upon the child and his or her family which compounds the scope of this problem.

Accomplishments

Although little can be done at present to prevent the onset and progression of the most common of these diseases, important research advances have been made.

In diagnosis, certain inborn errors of metabolism can now be diagnosed through blood studies (for example, Tay-Sach's disease). Also, the recent finding of elevated levels of the amino acid ornithine in the plasma of patients with a degenerative disorder (gyrate atrophy) of the retina and choroid has led to the identification of a single enzyme which may be at fault and to rational attempts at treatment. This is the first identification of a specific biochemical defect in individuals with this rare but significant form of retinal degeneration.

Once the specific biochemical defect responsible for an inborn error of metabolism is discovered, the way is clear for identifying carriers of the recessive gene by means of biochemical tests. Such measurements form the groundwork for rational family planning.

A specific biochemical abnormality has been discovered in the retinal degeneration associated with abetalipoproteinemia, and an effective treatment for this condition has been developed. Specific chromosomal abnormalities or faults have been noted in a developmental disorder, retinal dysplasia, and in the life-threatening ocular tumor, retinoblastoma.

Research Needs and Approaches

Accomplishing these objectives requires both improved understanding of the normal retina and finding the causes of developmental and hereditary retinal degeneration.

The Normal Retina. The close relationship between the retinal pigment epithelium and the photoreceptors must be considered in any attempts to explain generalized retinal degenerations. All proteins, carbohydrates, and other substances upon which the life of the retina depends pass across the pigment epithelium to nourish the cells of the outer retinal layers. In addition, many of the vital processes involving human vision require exchanges of nutrients, waste products, and other substances between these tissues. It is likely that a disturbance in these mechanisms constitutes the basic disease process in inherited retinal degenerations. Precise knowledge of these mechanisms is just now being gained, and research in this area must be expanded if further progress is to be made.

Development of Hereditary Retinal Degenerations.

Research in Humans. Establishing the precise nature of the disease processes underlying developmental and hereditary disorders can be pursued in several ways, including the use of the electroretinogram to improve classification of the various forms of these diseases and to help distinguish progressive degenerations from other similar appearing conditions.

Another powerful tool not yet fully exploited is fundus reflectometry, which permits the harmless study of visual pigments in the living human eye. It has already been used to detect specific visual pigment abnormalities in certain

diseases and could help provide the answers to important questions in such diseases as retinitis pigmentosa.

Animal Models. Difficulty in acquiring postmortem and postoperative human retinal tissue for laboratory study has impeded research progress. Animal diseases that resemble human hereditary retinal degeneration are therefore an important potential research resource, one that is just beginning to be explored. Animals with inherited retinal degeneration can contribute significantly to the development of safe and effective therapies through comparative observation of the effects of a new treatment on littermates. The establishment by NEI of a central animal facility for breeding and distributing these animal models to qualified investigators would further these important studies.

Specific Biochemical Abnormalities. Among hereditary retinal degenerations are several in which there are also systemic abnormalities. Studies of these conditions may lead to means of correcting the underlying biochemical defect. There is also need to search for biochemical abnormalities in retinal degenerations as yet unassociated with any known systemic defect. In addition, several studies show that retinal degeneration can stem from nutritional deficiencies, and further information on this subject should be actively pursued.

Biochemical Genetics. There is now good evidence that in certain diseases the unaffected carrier of a genetic disorder can be identified, and with newer and more sophisticated clinical tests, this type of information should be readily obtainable in the future. Studies should be pursued to improve the prospects of reducing the incidence of these disorders through genetic counseling.

Genetic Linkage Analysis. This technique is used to assign genes to specific chromosomes by identifying neighboring genes. It is based on knowledge that there is a strict order to the genetic map and thus an "invisible" gene can be recognized by its neighbors. It may be useful in determining the risk to as yet unaffected family members of a disease with delayed onset.

Diabetic Retinopathy and Other Vascular and Circulatory Abnormalities

One-sixth of all new cases of blindness is attributable to circulatory abnormalities of the retina, most of it associated with diabetes mellitus. Of an estimated 10 million diabetics in the United States, 300,000 are at high risk.

As mentioned earlier, the retina is nourished from two sources: retinal blood vessels, which have been extensively studied, and the blood vessels of the choroid, which have not. Diabetic retinopathy and other vascular diseases of the eye cause some blood vessels to close up, some to begin to leak, and others to grow new offshoots which then break and bleed. This can destroy sight, and unfortunately, once the retina has been hurt in this way, it cannot be repaired or replaced.

Other important diseases that affect retinal blood vessels include hypertension and arteriosclerosis, vascular occlusions, cystoid macular degeneration, sickle cell disease, and retrolental fibroplasia. Diseases affecting the choroid often affect the macular area, causing impairment of central vision.

Accomplishments

Over the past ten years, a safe and effective means has been developed to photograph the flow of blood in the retinal vessels of the living human eye. This

technique, fluorescein angiography, is now in wide clinical use and permits the ophthalmologist to identify a vascular abnormality as tiny as 1/100 of a millimeter. The success of this technique has stimulated efforts to discover an equally effective way to visualize the choroidal circulation. Progress to date is very promising.

New means of measuring blood flow and oxygen saturation within individual blood vessels are now being developed. These have implications that go far beyond ophthalmology including evaluation of the response of emphysema patients to treatment and improved management of heart failure.

The use of fluorescein angiography to visualize abnormal leakage of fluid from retinal vessels has made possible the development of a new approach to the treatment of these abnormalities: photocoagulation to seal off single, abnormal blood vessels and destroy areas of diseased retinal tissue that may stimulate their growth. In a controlled study of 1,700 patients, supported by NEI, investigators found that xenon arc or argon laser photocoagulation reduced by more than half the risk of blindness in moderate to severe diabetic retinopathy. Other research has shown photocoagulation to have beneficial effects in sickle retinopathy, a disease in which an abnormal form of the red blood cell blocks the retinal vessels and abnormal new blood vessels may subsequently grow.

The most common causes of retinal vein occlusion are thought to be arteriosclerosis and hypertension. The widespread use of fluorescein angiography has led to more frequent diagnosis of this condition.

The single largest cause of infant blindness in the early 1950's stemmed from the widespread use of oxygen to rescue premature infants suffering from life-threatening respiratory disease. Although by restricting the use of oxygen the incidence of retrolental fibroplasia has now been remarkably reduced, it still remains a significant cause of infant blindness because of the difficulty in precisely monitoring blood oxygen levels and of individual differences in retinal vascular sensitivity to oxygen.

Research Needs and Approaches

Fundamental Studies. Knowledge of *regional differences* in the anatomy and pathology of the retina and the choroid is fundamental to improved understanding of these diseases. For example, diabetic retinopathy tends to be most pronounced at the center of the retina, instead of in peripheral areas. Moreover, it mainly affects the retinal circulation; the choroidal circulation is generally spared for reasons which are not clearly understood. *Physiological studies* are needed to indicate how blood flow in the retina and choroid is controlled and to find noninvasive ways of measuring this flow. It must be found out why the macular capillary system is particularly predisposed to malfunction.

The cause and possible treatment of *leaking of fluid from retinal capillaries,* an early change in diabetic retinopathy, should be studied. Why some people develop these changes and others do not is not understood. Nor is it known why this condition is limited to the retina and does not occur in the brain. New anatomical research techniques can be brought to bear on these questions.

How and why new blood vessels are formed in diabetic retinopathy and other retinal vascular disorders is unknown. Recent studies have suggested that the diseased retina may produce a substance that initiates new vessel growth. Such an *angiogenic factor* has recently been shown in solid tumors.

The *pathologic clotting of blood* which is characteristic of diabetes may have a role in diabetic retinopathy and should be studied in detail. Drugs that could influence this process need to be investigated.

Most important, *basic studies* should be encouraged of the responsible mechanisms in diabetes mellitus, hypertension, and other conditions leading to aneurysm formation, increased vascular permeability, and vascular occlusion.

Comparative *pathological studies* of blood properties in people with and without diabetes may shed light on the early stages of diabetic retinopathy. *Improved tissue culture* methods will be valuable in clarifying the mechanisms responsible for development of small vessel occlusions and leakage. Enzyme systems that have been associated with diabetic complications in the lens can now be studied in cultures of retinal capillaries.

Clinical Studies. Improved understanding of the *natural history* of disorders such as diabetic retinopathy, branch vein occlusion, and sickle disease which follow a varied course are important to the evaluation of new treatments.

Randomized, controlled *clinical trials* of new treatments are often the only way a meaningful evaluation can be obtained. These studies incorporate such principles as standardized procedures, safeguards to avoid biased interpretation of results, application of advanced statistical methods to data analysis, constant monitoring of beneficial and harmful effects of treatment, and, above all, constant concern for the welfare of patients. The nationwide Diabetic Retinopathy Study of photocoagulation which has already demonstrated the therapeutic value of this technique is still in progress and should be continued and extended. Medical treatment of diabetic retinopathy and other vascular diseases should also be evaluated.

Myopia

There are two main types of myopia. In axial myopia the eyeball is too long, and rays of light focus in front of the retina. In refractive myopia the cornea and lens bend light rays too much.

Although close use of the eyes has been suggested as the cause of myopia, it is generally thought that genetic factors are largely responsible. The effect of use or other environmental factors, if any, may be additive.

About one-third of all adults in the United States are myopic—more than 70 million people. While most of these are cases of simple myopia which can be corrected with eyeglasses or contact lenses, it should be noted that Americans spend over $1 billion each year for corrective lenses and that some young people fitted with eyeglasses develop psychological problems as a result. More important is the small but significant percentage of myopic persons who are severely afflicted. Some will develop degenerative changes in the retina, choroid, and sclera, which can lead to partial or complete loss of vision.

Accomplishments

Several recent findings have set the stage for a new series of investigations into the causes, prevention, and therapy of myopia. In three separate studies, atropine and atropine-like drugs have been reported to arrest or produce partial regression of myopia in a high percentage of cases. However, these studies were of short duration, and the results have not been widely accepted.

In addition, experimental myopia has been induced in monkeys by making them use their eyes for near vision for prolonged periods. The developing myopia was stabilized after application of atropine to the eye.

An important new laboratory model for myopia has been produced by surgically fusing the eyelids of one or both eyes of newborn animals. In the

monkey, sutured eyes increased in length after one and one-half years by 25 percent compared to untreated eyes. Interestingly, the myopia became stationary after the eyelids were opened.

It has also been observed that glaucoma in young children leads to enlargement of the eye and thus to axial myopia. A laboratory model is available for this type of myopia since rabbits with congenital glaucoma also develop secondary myopia.

The high frequency of myopia in the U.S. population and the increased incidence of retinal detachment and macular degeneration in patients with high degrees of myopia make it imperative that substantial efforts be put into future investigations in this area.

Research Needs and Approaches

Because the sclera and perhaps the vitreous body are the tissues primarily affected in progressive or pathological myopia, any attempt to understand this condition must proceed on the basis of a better understanding of their *normal structure and function.* An important subject for research is why the sclera, which normally resists stretching, fails to resist it in high myopia. Changes in the vitreous body are also of prime importance because they lead frequently to retinal detachment in highly myopic eyes.

Further *research in animals* is needed to determine if myopia can be regularly and predictably induced by eyelid fusion and to discover how this occurs. In addition, there is need to ascertain whether other ocular changes, particularly degenerative changes, occur in animals as they do in people with severe myopia. If so, this animal model may be useful for studying the cause and treatment of both degenerative and simple myopia.

Clinical research should proceed along *medical and surgical lines.* If it can be proved that the daily use of atropine drops can retard the development of myopia, this would be of great clinical importance. The Council believes this matter to be of sufficient importance and the reported studies to have shown sufficient promise to warrant substantial further emphasis.

Surgical approaches for severe progressive myopia have shown variable results. Because studies of these approaches have often been poorly controlled and not well documented, they should be perfected in laboratory animals; thereafter, their worth in humans should be carefully evaluated and documented.

The relationship between systemic deficiencies and myopia should be studied to determine whether a common tie may be an inborn error in the structure of scleral collagen or of one of the enzymes that regulates and maintains the production of normal collagen.

Tumors

Tumors of the eye have an importance that surpasses their frequency, for not only can they cause blindness, they can cause death as well. Metastasis is common even with radical surgery.

Internal tumors of the eye principally arise from the retina and the uvea. Other eye tumors may originate in areas such as the lids, the conjunctiva, and the orbit. Two basic types of tumor are of importance for the following discussion: retinoblastoma and malignant melanoma.

Retinoblastoma is the most common ocular tumor occurring in children. In the United States and Western Europe, approximately one in every 23,000 live births is afflicted with this condition, and the frequency appears to be increasing. The costs in suffering and economic loss to the individual and to society are high: even

though it can be treated with up to 90 percent effectiveness, retinoblastoma often affects both eyes and generally occurs within the first three years of life.

Malignant melanoma usually is restricted to one eye, but in the significant number of patients who develop metastatic disease, there is an agonizing, prolonged terminal course.

Accomplishments

Although death can often be prevented by diagnosing ocular tumors early, treatment frequently involves surgical removal of the eye. Eye tumors are most often discovered after the victim notices something is wrong and seeks professional attention. The ophthalmologist then diagnoses the presence of a tumor by a careful eye examination. Other good diagnostic methods are available; these include, for intraocular tumors (tumors within the eye) fluorescein angiography, ultrasound, ^{32}phosphorus (^{32}P) radioisotope techniques and, in selected cases, biopsy or tapping of the anterior chamber fluid for examination. For diagnosing tumors outside the eye, arteriography, venography, "CAT" or "EMI" scans (special X-ray techniques) and ultrasonography may be usefully employed.

Disagreement exists over the relative merits of various treatments for eye tumors, particularly regarding the value of removing tumors from the eye compared to removing the whole eye.

Work on eye tumors promises to benefit other fields of tumor research, because the eye offers unparalleled opportunities for observation, access, and isolation of the tumor. It should also be noted that the eye, as a frequent site for metastasis, affords an invaluable chance to measure precisely the visible effects of different types of systemic cancer therapy.

Research Needs and Approaches

The most promising lines of research at present involve:

- The search for a viral etiology of ocular tumors.
- Immunologic studies to improve diagnosis, surveillance, and treatment of ocular tumors.
- Epidemiologic studies regarding the diagnosis and treatment of ocular tumors.

Evidence suggests that viruses may play a role in the etiology of many types of human cancers. The enzyme "reverse transcriptase," recently identified as the key to how viruses interact with hereditary material in cells, has been found in retinoblastoma and in other malignant tumors of the eye.

One virus-like particle reported in some spontaneous tumor cells is the DNA herpes virus, and herpes-like inclusion bodies have been noted in the cornea and limbus of the eye. The tumor-causing potential of herpes simplex virus types 1 and 2 inactivated by ultraviolet light has been convincingly demonstrated. However, it is not known at present if the herpes viruses or any other viruses cause human cancer.

One important finding being explored is a chromosomal abnormality that has been associated with retinoblastoma. Approximately 25 percent of patients reported with this abnormality have retinoblastoma. Although it is likely that a

gross chromosomal abnormality causes only a relatively few cases of retinoblastoma, it is possible that a more subtle defect causes the majority of cases. Immunologic techniques are being used to explore possible evidence that adenoviruses may induce human retinoblastoma.

The search for possible viral etiology of ocular tumors should be a multidisciplined approach involving morphology, molecular biology, enzyme chemistry, immunology, and virology. A similar approach should be undertaken for a broad-based investigation of the immunology of patients with ocular tumors.

A coordinated, cooperative study combining the retrospective and prospective experience of the country's major ophthalmic centers would be useful in evaluating methods for diagnosis and treatment of ocular tumors. Treatment to prevent metastasis is also an area of deep concern, as are questions about the relationship of certain features of the tumor, such as its size, in relation to prognosis.

Macular Diseases

Diseases of the macula affect the central area of the retina, the region of high visual acuity, and in many cases lead to disastrous loss of vision. Each year, over 165,000 additional people in the United States develop macular disease. For some, this leads to blindness. Many others have a lesser degree of impairment, but their ability to read or see small objects clearly is lost.

The most common type of macular degeneration is the "senile" form affecting the elderly, often turning the so-called "golden years" into a time of frustration and anguish. A juvenile form affects people under age 20, severely hampering the learning process and choice of career. Other kinds include central serous macular disease, toxic effects on the macula from certain drugs, and those resulting from a host of other causes.

Accomplishments

Recent research on macular diseases has permitted a better distinction among the various categories of the disease, improved correlations between clinical observations and laboratory findings, and new techniques for diagnosis. Possible treatments for some forms are being evaluated.

The distinct categories of macular disease have been recognized only in the past ten years. An earlier classification simply by age of onset (senile or juvenile) has now been improved. For example, several types of senile macular degeneration are now recognized, each representing a distinct pathophysiologic mechanism.

Improved knowledge of macular disease has resulted from study of eyes removed at autopsy which have known and documented macular abnormalities. The cause of some types of macular degeneration can now be localized to specific tissue layers.

Diagnosis of macular disease has been greatly improved through fluorescein angiography which also permits detection of abnormalities other than those of the blood vessels, such as faults in the pigment epithelium.

Treatment of macular disease has been enhanced by the development of the argon laser, which permits, in selected cases, the closing off of abnormal blood vessels before they bleed or the sealing of tissue breaks to stop leakage of blood components into retinal vessels. The effectiveness of this therapy is still being investigated.

Research Needs and Approaches

Basic Laboratory Studies. Of primary concern are the anatomical changes in the retina, retinal pigment epithelium, and choroid, which occur during aging. In particular, the effects of aging on the composition and metabolism of the collagen which constitutes Bruch's membrane, the basal membrane lying between the retina and choroid, needs to be studied.

Although it is well-known that the *macular region is predisposed to various degenerative changes,* the reasons for this are not clear. An exhaustive comparison of the differences between the central and peripheral retina may provide important clues to the macula's unique susceptibility.

In the past, *clinicopathologic correlations* have improved the categorization of macular diseases; they should be continued. However, to apply modern research techniques, the present way of obtaining eyes—postmortem or at surgery—must be drastically altered. A coherent plan of action is needed in which eyes with specific characteristics are systematically collected and distributed to qualified investigators who are following defined research protocols.

Another area of basic laboratory study involves the *physiology of the macular region*—in particular, the physiologic dependence of the retina on the retinal pigment epithelium. Improved understanding is needed of the normal barriers that restrict certain substances circulating in the bloodstream from entering the retina except via the pigment epithelial cell. The requirements for maintaining such barriers during a lifetime also need to be understood.

Likewise, *angiogenic factors* must be studied in more detail because there is now reason to suspect that a substance which induces formation of new, abnormal blood vessels is responsible for the production of choroidal neovascularization. The development of new *dye methods* to study the choroidal circulation in a manner similar to that in which fluorescein angiography is used to study retinal blood flow should be continued. In addition, means other than marker dyes should be sought to achieve the same result.

Improved diagnosis of macular disease should also be sought, including, in particular, better means to measure objectively the visual response to a given visual stimulus (*psychophysics*). Improved *electrophysiological* devices and techniques are needed to help in the detection of isolated macular abnormalities. The *biochemical study* of the retinal pigment epithelium and choroid in tissue culture should be pursued as well as the susceptibility of these tissues to *toxic chemicals.*

A major stumbling block in fundamental studies of macular diseases is the lack of available *animal models* of macular degeneration. Recent discoveries of macular disease among baboons justify a widespread search of animal colonies throughout the world to find other types of retinal degeneration.

Clinical Studies. The foregoing fundamental laboratory studies must be complemented by clinical studies of the natural history of different types of macular degeneration. These can provide a more complete understanding of the various courses followed by these diseases and provide a basis for evaluating the effects of proposed new treatments. The ongoing collaborative Diabetic Retinopathy Study, mentioned earlier, provides a model of the type of study in which the treatment of macular disease could be evaluated scientifically.

Retinal Detachment

Any separation of the two layers of the retina—the neural retina and the pigment epithelium—is called retinal detachment. This condition can and often

does cause permanent impairment of vision. It is estimated that over 25,000 cases of retinal detachment are diagnosed yearly. Many lead to markedly decreased vision and functional loss of the eye. Treatment to reattach the retina is successful in approximately 70 percent of the cases due to retinal breaks followed by the restoration of at least partial vision. But because the success rate in other types is considerably lower, each year a minimum of 6,000 people lose most of their useful vision in at least one eye from this condition. Approximately 15,000 recover partial vision and 4,000 fully recover following treatment.

The causes of retinal detachment are diverse, such as abnormal traction on the retina in the direction of the vitreous humor, or tears or holes that develop in the retina. It may occur without apparent cause, be related to other eye diseases or conditions such as a high degree of nearsightedness, or follow trauma. In all cases, loss of sight is due to fluid accumulating under the retina.

Accomplishments

In the past 25 years, the accuracy of diagnosis of retinal detachment has improved considerably due to new and improved optical techniques such as binocular ophthalmoscopy. Thanks to such techniques, treatment has become much more effective; it has been further improved with the advent of scleral buckling operations that reestablish the anatomical position of the retina and of improvements in diathermy, cryosurgery, and photocoagulation. As a result, the hospital stay for retinal detachment has been cut from an average of four weeks to an average of one week.

Current research supported under National Eye Institute grants is focused on further improvements in diagnosing and treating retinal detachment. Much more research needs to be done to clarify the pathogenesis of this condition.

Research Needs and Approaches

Diagnosis. Improved diagnosis of retinal detachment will result from further research in *optical methods.* These include instruments which can visualize, measure, and photograph the vitreous body and the various retinal layers with greater clarity.

Today, *electrical and functional studies* of the retina are used to determine its potential for recovery. Three techniques currently available are electroretinography (ERG), visually evoked response (VER), and electro-oculography (EOG). These should be developed further and, in particular, refined to enable determination of the functional potential of specific areas of the retina, such as the macula. In addition, psychophysical procedures need to be improved to afford accurate and replicable techniques for helping establish the degree of functional impairment of the detached and of the reattached retina plus the potential for further visual recovery.

Pathogenesis. Research in pathogenesis should receive the most attention, particularly in three areas:

- *Adhesion of the retina to the choroid.* It is believed that retinal adhesion weakens well before retinal detachment occurs. In addition to the basic processes involved, it is important to study the effects of diathermy, cryoapplication, and photocoagulation on retinochoroidal adhesion.

- *The relationship between the vitreous and the retina.* Detailed knowledge of this relationship may make it possible to prevent preretinal scarring, the basic cause of most incurable retinal detachments.
- *The blood-retina barrier.* Disturbances in the blood-retina barrier are probably the main underlying cause of retinal breaks and certain types of retinal detachment.

Treatment. Research is needed to evaluate the role and value of surgically-induced chorioretinal scars in reattaching the retina, to improve scleral implants, to find means of treating severe cases of rhegmatogenous retinal detachment (those detachments resulting from large tears, with massive preretinal retraction, or those due to abnormalities in the structure of the optic nerve head or choroid), and to improve vitreous surgery, either with or without tissue removal.

Prevention. The importance of research on prevention is indicated by a ten-year survey in Israel that indicated that the introduction of preventive retinal surgery has not decreased the incidence of retinal detachment. Research needs include identifying the best method of prophylactic treatment, selecting the most suitable cases for such treatment, and determining the biochemical and anatomical factors that predispose to retinal detachment in certain developmental, systemic, and inherited anomalies. It would also be useful to elucidate the relationship between intraocular blood circulation and retinal detachment because there are indications that retinal and choroidal circulatory deficiency is the common denominator in many cases.

The need for animal models is as important for this disorder as for several others mentioned elsewhere in this volume. Needed animal models include those that are known to be naturally predisposed to retinal detachment and those which can be produced by noninvasive manipulations. In addition, isolated mammalian eyes perfused with whole blood are also useful models.

Inflammatory Disorders

Inflammatory disorders of the retina and choroid are numerous and highly destructive. They commonly affect not only the retina and the choroid but the vitreous body and the front portion of the uvea as well. Such diseases are frequently blinding and, in certain cases, painful. Commonly referred to as "uveitis," these disorders may affect many ocular structures other than the uvea itself.

Some inflammatory diseases arise from infections, such as toxoplasmosis and histoplasmosis, and others from immunologic insults. Whether the latter are initiated by trauma or by infection, they are self-sustaining and continue to plague the patient long after the trauma has been repaired or all traces of the original infection have disappeared. These disease processes are generally thought to represent autoimmune phenomena in which the body's immunologic defense system is turned against its own tissues.

In addition to the clearly infectious and the clearly noninfectious categories of inflammatory diseases, a third type is suspected of being infectious in origin, but so far has evaded specific etiologic diagnosis.

In 1972 approximately 67,000 Americans were estimated to have severe visual impairment from uveitis, of whom 23,000 were legally blind. These figures do not take into account the less extreme forms of ocular disability associated with inflammatory diseases, which include severe pain, light sensitivity, floating spots, and some degree of visual impairment for months or years.

Accomplishments

Basic and clinical research has produced extraordinary advances in the diagnosis and treatment of inflammatory diseases.

Diagnosis. Until recently, diagnosis of ocular inflammatory disease had to be made indirectly through blood tests, skin tests, x-rays, and the like. Recently, a number of direct approaches have been developed. One, removal of a small sample of aqueous humor, has permitted the isolation and identification of bacteria or the demonstration of specific antibodies. Others are fluorescein angiography which helps visualize vascular pathways and, most recently, fundus reflectometry. However, in most cases, the basic mechanisms underlying ocular inflammatory disorders remain unknown.

Treatment. Improved forms of therapy have been developed mainly with the aid of animal models. These include the use of several drugs such as clindamycin and 5-fluorocytosine for the treatment of toxoplasmosis and *Candida* infections, respectively, and the surgical removal of severely inflamed vitreous tissue.

Notwithstanding the dangers of using immunosuppressants to excess in certain types of infectious diseases, these agents have proved to be of some value in treating steriod-resistant or otherwise intractable inflammatory diseases in which immune mechanisms are thought to play a major role.

Research Needs and Approaches

Improved Diagnosis. Improvements in diagnostic techniques should be pursued, particularly those which will permit accurate identification of the offending organism or basic pathogen. These include methods for *direct diagnosis from ocular tissues.* For example, it is possible to remove vitreous fluid through a hypodermic needle inserted into the eye at the pars plana, the flat part of the ciliary body adjacent to the retina. Although there are certain dangers associated with this technique, potential rewards are high; more extensive use seems justified in the future. Moreover, appropriate therapy in many cases involves the use of toxic drugs administered intravitreally or intravenously, but these can only be justified if a precise etiologic diagnosis has been made beforehand.

The use of *chorioretinal biopsy,* though not without risks, would permit direct histopathologic examination of affected tissues. This would help solve many diagnostic problems, particularly those concerned with distinguishing inflammatory from degenerative conditions.

The need for definitive *clinicopathologic studies* is evident. This field is still in its infancy, and institutions capable of performing reliable light and electron microscopic studies of enucleated uveitis eyes should be funded for additional work in this area. A concentrated effort must be made to form a registry of well-studied uveitis patients, and collaborative investigations should be encouraged.

Where clues to the nature of a given inflammatory disease have been discovered, they should be followed up by attempts to produce these diseases in the eyes of appropriate *laboratory animals.* Certain natural models already exist such as the cat for toxoplasmosis. Animal models are important both for determining the natural course of the disease and for discovering the effects of various forms of drug therapy.

Controlled, randomized trials of drug therapy to enhance the evaluation of treatment should be attempted in situations where promising leads have been supplied by animal experiments and where preliminary trials on humans indicate

that the drug is both safe and efficacious. Few of the drugs currently in use for the treatment of inflammatory diseases of the retina and choroid have been subjected to such testing.

Uveal Tract

The uveal tract is the middle coat of the eye, sandwiched between the scleral coat and the retina. It is represented in the back part of the eye by the choroid and in the front of the eye by the iris. Between the iris and the choroid is the ciliary body, composed of secretory cells which produce the aqueous humor, and the ciliary muscle, which controls accommodation (focusing) of the lens. Bruch's membrane is a thin elastic sheet separating the retina from the capillary network of the choroid.

The uveal tract plays an important supporting role for many of the structures of the eye. Unfortunately, it is often at risk. Circulatory disorders, inflammations, and macular degeneration are among the most common ocular diseases that spring primarily from malfunction of the uveal tract, and they are discussed elsewhere in this report. It should be noted, however, that the posterior part of the uveal tract is singularly vulnerable to debilitating changes associated with aging. Some degree of sclerosis in choroidal vessels is observed in 50 percent of people over age 60. In a small but tragic minority, abnormal vascular channels that breach Bruch's membrane and contact the retinal pigment epithelium are seen. Because such changes underlie macular degeneration, the leading cause of new blindness in Americans over age 65, concern with uveal tract problems focuses on basic anatomical and physiological aspects of aging.

Accomplishments

Significant research advances have been made in recent years toward understanding the development, structure, function, and pathology of the uveal tract.

It is now known that the capillary network of the choroid, called the choriocapillaris, nourishes the entire retina in the central foveal region and the outer retinal layers in the rest of the eye. This network is prone to several hazards. It traps foreign material, produces new blood vessels, and is subject to debilitating aging changes. The choroid is a prime target in the body for inflammation and metastatic tumors.

Until recently, it had not been possible to study the choroidal vascular system in living patients because the pigment epithelium obscures it completely from view. As a result of the development of choroidal angiography, it is becoming possible to observe choroidal vessels in normal and progressive disease states in living patients. This is similar to the method by which retinal circulation is made visible by fluorescein.

It is also now known that Bruch's membrane acts as a separator, a sieve, and a support. As a barrier between the retina and the choroid, its importance is underscored by the havoc that follows its failure. Vascular growths that transgress Bruch's membrane exert highly deleterious effects on the retina, particularly on the macula. Bruch's membrane must also act as a sieve which permits molecules up to a considerable size to pass through it for nourishment of the retina. Finally, Bruch's membrane provides essential support to adjacent tissues.

The ciliary body has two essential functions: to produce aqueous humor and to participate in accommodation of the lens. The aqueous humor brings essential

nourishment to the lens and cornea, carries waste products away, and maintains the intraocular pressure at an even level.

The iris functions as a movable diaphragm. Its detailed ultrastructure and the method by which it is controlled by the autonomic nervous system are known. Studies have also indicated how the pupil can be safely and reversibly dilated with drugs for examination, treatment of inflammations, and surgery. The iris also permits the aqueous humor to flow from the posterior chamber to the anterior chamber in order to maintain the intraocular pressure.

Research Needs and Approaches

Anatomical studies should focus on learning why the region of the choroid underlying the macula is predisposed to certain types of degenerative diseases, on investigating changes in the small choroidal blood vessels and in their environment during aging, and on studying such abnormalities as breaks and calcification of Bruch's membrane, particularly during aging.

Physiological studies are merited to determine what normally controls the extent and location of blood flow to the choroid as well as the changes in blood flow that result from elevated intraocular pressure or from systemic hypertension. Studies of the nomal flow of fluid between vitreous, retina, and choroid are essential to understanding conditions in which the flow goes awry.

Biochemical studies of the choroid in tissue culture could help in determining the biochemical basis of new vessel growth in choroidal disease.

Clinicopathologic studies should be undertaken to correlate clinical records with postmortem laboratory findings. This could lead to more specific therapeutic approaches. Of particular importance is study of alterations in Bruch's membrane that may play a role in macular disease.

Finally, increased awareness of the importance of the ocular immune response in eye disease as well as of the uvea's predilection to inflammation mandates a substantially increased effort in *ocular immunology*.

Vitreous Humor

When a retinal blood vessel breaks and blood flows into the vitreous humor, vision is immediately impaired. Moreover, blood in the vitreous humor acts as an irritant, causing the formation of a scar which itself can hamper clear vision, but more seriously, by contracting can detach the retina from its normal position. This course of events is characteristic of several diseases that result in blindness, including diabetes mellitus; traumatic vitreous hemorrhage; in young adults, sickle cell retinopathy; and in infants, retrolental fibroplasia. Most important, the vitreous body is believed to play a major role in the etiology of most primary retinal detachments.

Accomplishments

The basic nature of the vitreous body is well established; however, the functions of many of its constituent parts are only partly understood. For example, the function of vitreous cells and the physiological role of the vitreous aside from its keeping the center of the eye transparent have not been fully explained.

During the past 15 years, vitreous examination has been improved, and vitreous surgery has developed considerably. The present strong emphasis on disease-oriented vitreous research is largely due to the development of instruments that permit mechanical extraction of the vitreous (vitrectomy). These studies, among which is a national multicenter study sponsored by NEI, the Diabetic Retinopathy Vitrectomy Study, are seeking to determine the best means and times for treatment, to identify the indications for vitrectomy, and to document in detail the complications of this procedure in a wide variety of disorders. Current research also includes histological studies and attempts to identify vitreous substitutes.

Research Needs and Approaches

Better understanding of the nature and functions of the vitreous body will be promoted by:

- Studies of the physical state of the vitreous body, with particular attention to the pathological changes caused by damage to its structure.
- Studies of the role of cells in the vitreous body, particularly in the synthesis of important metabolic substances.
- Studies of the immunological role of the vitreous body in persistent uveitis.
- Studies relevant to diabetic retinopathy that would define the "route of entry" of cells and molecules from the blood, and the vitreous body's metabolic interaction with adjacent tissues.
- Better understanding of how the vitreous normally regenerates itself.

Research in the management of vitreous diseases should focus on:

- Pathological studies of newly formed membranes and blood vessels within the vitreous that characterize many retinal diseases.
- Documentation of the long-term effects of vitrectomy.
- Attempts to improve surgical treatment, particularly after severe ocular trauma and penetrating injuries.
- The long-term effects of vitreous substitutes or implants that may be useful in treating severe cases of retinal detachment.
- Study of the efficacy and risks of direct injection of antibiotics into the vitreous to treat intraocular infections.

Visual Cells and Pigment Epithelium

Because the visual cells and pigment epithelium are basic elements in the visual process, their death or malfunction is at the root of many blinding diseases. Most of these—developmental and degenerative disorders, such as retinitis pigmentosa and macular degeneration, nutritional and metabolic deficiencies, blood-borne abnormalities, drug toxicity, and a variety of conditions associated with or leading to retinal detachment—have been discussed in previous sections.

The photoreceptor cells—rods and cones—are the most specialized in the visual system. The outer segments of the rods and cones that receive and transmit the

visual stimulus are imbedded in the pigment epithelium. Separation of the two leads to loss of vision.

Accomplishments

Past research successes have provided a solid base of information from which future improvement in clinical care can evolve. These have included extraordinary advances in understanding the structure, chemistry, electrophysiology, and cellular biology of the photoreceptors and pigment epithelium. It is now understood that in normal metabolism outer segment membrane discs are constantly shed and replaced, and that the pigment epithelium not only helps to nourish the retina but digests the shed discs.

Research Needs and Approaches

In the past three years, it has become clear that, at least in the case of rods, light plays a pivotal role in controlling the process by which discs are renewed and shed from outer segment tips. Further work to understand the biochemistry and mechanics of this effect is necessary. Once they are shed, these fragments are engulfed and digested by the retinal pigment epithelium. Study of these processes must be extended to determine how they are controlled and what may go wrong with the system. These studies should include investigations of nutritional factors, genetic variations, and how light affects the structural composition of the visual cell membranes.

Studies of the incorporation of rhodopsin, the photopigment which transmits the light stimulus, within the outer segment membranes are in progress and hold promise. The position of rhodopsin within the membrane, the location of its functional sites, and how it interacts with membrane lipids are being determined by sophisticated laboratory techniques.

Studies of how light triggers the visual process by altering the structure of rhodopsin, of the possible role of calcium in visual transduction, of energy production and utilization in different parts of the visual cell, and of intracellular messenger substances are rapidly burgeoning, with many very essential questions remaining to be answered.

How and under what circumstances and influences visual pigment regenerates after being altered by light is worthy of continued and expanded study. In particular, how vitamin A is transported to the retina and the specific roles of substances and chemical systems within the pigment epithelium and visual cells in the transduction of light energy into visual impulses merit further study.

Here, as in other areas, research is stymied by inadequate programs for breeding and distributing the numerous existing animal models of inherited human diseases of the visual cells. For example, in animal models of retinitis pigmentosa, certain photoreceptor cell bodies survive despite the degeneration of others, and vision is maintained to a surprising degree even in advanced disease. Such residual capacity may exist in humans with retinitis pigmentosa, and ways to develop it should be sought through further animal studies.

The study of the selective degeneration of photoreceptors and pigment epithelium caused by drugs and poisons has been useful in determining the vulnerability of retinal cells and in defining critical areas for future research. Indications that light in excess of that in an animal's normal habitat can destroy photoreceptors suggest the need for further studies of the effects of light on patients with macular degeneration and with retinitis pigmentosa.

Retinal Organization and Visual Adaptation

The retina is much more than an array of photoreceptors. The visual signal generated by the rods and cones must pass through a complex neural network made up of four different types of nerve cells whose precise connections are still unknown and which are actually a part of the brain located within the eye. Thus, much of the neural processing of visual signals occurs within the retina, and an understanding of retinal mechanisms and organization is requisite to any understanding of vision. Conversely, any understanding of the retina also provides clues to brain mechanisms. In fact, more and more brain researchers are turning to the retina because, in reality, it is an accessible piece of brain tissue.

The impact of diseases of the retina on the individual, the family, and society at large has been presented elsewhere in this volume. Fundamental to the prevention, diagnosis, and treatment of these diseases is a basic understanding of retinal organization and visual adaptation.

Accomplishments

The retina may be the best understood part of the vertebrate central nervous system. However, much more must be learned before the retina is understood well enough to make a significant impact on eye disease prevention and treatment. A good deal of this information has been derived from studies on cold-blooded vertebrates, but research must be extended to mammals and humans.

Research Needs and Approaches

Studies of the *retinal anatomy* with the aid of the electron microscope are identifying more and more of the junctions between retinal cells, permitting the production of qualitative diagrams of the visual pathways through the retina.

Studies of *retinal function* require precise, quantitative "wiring" diagrams of vertebrate retinas. These are virtually within reach with present techniques. Precise quantification of the relationship between visual function and the *electrical activity of the retina*, which is now possible, is essential to an understanding of retinal activity. Recording electrical signals from single retinal cells through use of glass micropipettes has revolutionized understanding of the *intraretinal mechanisms* by which visual information is processed and has made this area one of the most active and exciting in all vision research. As yet, almost all studies have been done in cold-blooded vertebrates. Studies in mammals are just beginning and should be increased.

In addition to using electrical measurements to monitor transfer of information through the retina, this process needs to be defined in terms of the chain of *biochemical events* that occurs when the retina responds to a change in illumination. This work in the retina is likely to be the source of major new advances in the molecular biology of nerve tissue.

Additional areas of research importance are the *pharmacology of the retina* (with particular emphasis on neurotransmitters) and *visual adaptation*, the ability of the visual system to adjust its sensitivity to prevailing light. Studies of visual adaptive mechanisms are providing clues to defects in certain night blindness conditions.

The eyes of *invertebrates* can permit certain important studies which are more difficult with the vertebrate retina. This is because of the large cell size, accessibility,

and, sometimes, simple organization of invertebrate eyes. This research has made important contributions to the understanding of visual mechanisms in general and should continue to be supported primarily in those circumstances where the use of vertebrate retina is not appropriate.

Special Areas of Future Interest

Beyond but related to the opportunities discussed in the foregoing sections are several special areas which are important but have yet to receive the recognition they merit. They are:

- Toxic and Environmental Disorders
- Low Vision
- Retinal Regeneration and Transplantation
- Tissue Acquisition and Distribution: Human Donor Eyes and Animal Models

Further discussion among vision scientists, representatives of the National Eye Institute, and other interested parties is required in order to define a specific course of action in each of these areas. However, some preliminary considerations follow.

Toxic and Environmental Disorders

Clinical evidence indicates that many drugs, chemicals, and environmental factors can damage the eye. The incidence of such disorders, however, is unknown.

The problem of toxicity is two-fold. First, the retina is unique among body tissues in its great vulnerability to toxic and environmental insult. The retina has special nutritional requirements and a delicate physiology, and the environment in which it operates has a surprisingly narrow tolerance for change. Therefore, toxic or environmental agents harmless elsewhere can and often do exert deleterious effects.

Second, studies of toxic and environmental effects on the retina are generally performed outside the eye research community, often by individuals and organizations without special knowledge of the eye. Toxic effects of drugs on the eye may not even be recognized by the clinician during a routine eye examination. Although a few government-sponsored research projects on toxic and environmental effects do pay attention to the eye, the scattered activities that currently exist are inadequate in terms of the breadth and complexity of the problem.

Suggested Research Approaches

- Adequate testing for retinal toxicity of all new drugs prior to their general release.
- Stringent follow-up of individual case reports of retinal toxicity resulting either from drug use or from substances included or added to certain foods.
- Determination of tolerable levels of exposure to ambient light, particularly for individuals with retinal degenerative diseases.
- Setting of acceptable standards for exposure to different types of radiation.

- Improved methods of animal testing for toxic and environmental factors that will be relevant to man.
- Assessment of drug effects in the developing retina.
- Evaluation of methods to determine the clinical significance of drug-related changes in retinal function.
- Determination of the mechanisms by which drugs damage the eye.

A number of policy and administrative considerations must be resolved before a research program in this area can be developed and supported. Among these are:

- The role of the National Eye Institute (where and how the NEI should participate).
- The capabilities of the NEI (additional staff and financial resources).
- Mechanisms of support.
- Level of support.

Low Vision

Disabling visual impairment that falls short of total blindness has not attracted the concern it warrants. Although many public and private agencies and individuals are responsible for the welfare of the visually handicapped, research in this area has been sparse. No single center and no single training program is devoted to the orderly development of ways to improve the visual performance of the partially sighted. However, those few research programs which have been conducted in the past to improve the visual performance of the partially sighted clearly indicate the merit of such efforts.

To enhance the visual use of the impaired retina, and to improve the image generated through the clouded cornea or lens, attention should be directed to:

- The utility of bright illumination.
- Improved use of the peripheral retina.
- The evaluation of new magnification devices (including units that incorporate closed-circuit television) in combination with lighting modification and contrast changes.
- Determination of the full potential and limits of laser-generated images.

Retinal Regeneration and Transplantation

Whatever success is achieved in the efforts recommended elsewhere in this report, there now exists and will continue to exist the need for some means of renewing or reorganizing damaged eye tissue. However, renewal, whether by repair or replacement of any of the linkages in the human visual system, remains a long-term goal. Two interrelated possibilities stand out: retinal regeneration and retinal transplantation.

Retinal Regeneration

Total regeneration of the neural retina from the pigment epithelium occurs in some nonmammalian species, the salamander for example. From interspecies

studies, it appears likely that the ability to regenerate a functional neural retina has been lost in several evolutionary steps. If these steps were identified, it might be possible to restore the mammalian retinal pigment epithelium its lost ability to form a new neural retina.

The axons of ganglion cells give rise to the optic nerve. Capacity for renewal of ganglion cells varies among vertebrate species. Knowledge of the regeneration process is not advanced sufficiently to explain why differences exist among species. Comparative studies to learn more about this subject are certainly warranted.

Retinal or Ocular Transplants

There is not any near-term prospect for successful mammalian eye transplants. However, success in transplanting the eye in lower vertebrates indicates that this subject, which is of overriding clinical importance, merits research attention. Limited and thoughtful laboratory effort in the direction of retinal and ocular transplants should be undertaken.

Tissue Acquisition and Distribution: Human Donor Eyes and Animal Models

Progress in understanding eye diseases depends on the acquisition and appropriate study of human and animal tissues. Because at present it is not feasible to biopsy the retina and choroid routinely, it is essential that human eyes removed because of malignancy or taken after death be made available for scientific study. In addition, animals with eye pathology similar to that occurring in humans should also be more widely distributed.

The needs for animal and human tissues are interrelated. Discovery of a specific defect in animal eyes can pinpoint the need for appropriate studies of humans. The existence of animal models may also permit practical trials of therapy in animals that could have important applications to such human eye diseases as retinitis pigmentosa and other hereditary retinal degenerations, diabetic retinopathy, uveitis, and retinal detachment. In searching for the cause of a disorder, there is no substitute for studying the tissue it affects.

At present, the supply of human eyes is inadequate to meet research needs. However, there is evidence that with proper advertising and collection procedures, human eyes with specific pathology can be obtained. In order to be of full value, donor eyes should have the type and degree of disease fully documented throughout its course and should be preserved in a manner appropriate to a specific research study.

In the case of animal models, the cost and effort involved in acquiring, caring for, breeding, and distributing animals overwhelm the average researcher. Only a national program, such as that exemplified by the National Eye Institute's current contract for the production and distribution of a type of rat with a hereditary retinal degeneration, can succeed.

It is therefore imperative that animal models and donor eye programs be given a new dimension and new emphasis. The relatively small pilot efforts of the past should be expanded to meet the enlarged opportunity of the present and future. This will require a national effort which demands good planning and organization as much as adequate funding. Such an effort is essential to further progress in the fight against retinal and choroidal diseases.

Corneal Diseases

Introduction

The cornea is the transparent structure at the front of the eye that, by means of its convex surface, acts as a powerful lens. The cornea contains no blood vessels but is completely nourished by the fluids that bathe it: the tear film on its outside surface and the aqueous humor on its inside surface. Almost twice as thick at its periphery as it is at its center, the cornea can be divided into five layers: the epithelium, Bowman's membrane, the stroma, Descemet's membrane, and the endothelium. Although the epithelium has the power to regenerate itself and heal rapidly without scarring, injury to the deeper structures usually results in formation of an opacity.

In the National Eye Institute's *Corneal Diseases* program, the following six subprograms have been established:

- External Infections and Inflammatory Diseases
- Dry Eyes and Tear Abnormalities, Epithelial Disorders, and Drug Delivery
- Refractive Problems and Contact Lenses
- Corneal Edema, Dystrophies, and Inherited Disorders
- Corneal Transplantation and Stromal Injury and Repair
- Tumors and Other Lid, Conjunctival, and Orbital Problems

Importance

Over 2 million cases of corneal disorders and diseases occur each year in the United States, and over 1.7 million injuries to the cornea or external eye are also recorded annually. These account for 62 percent of the total incidence of all acute and chronic disorders, diseases, and injuries to the eye. Every year these conditions account for over 100,000 hospital days and for over $12 million in surgical costs alone. Corneal problems other than refractive errors necessitate approximately 10 million annual office visits for professional eye care; this is one-third of all visits for professional eye treatment or care.

Disorders which require only optical correction are also important. Virtually everyone over the age of 45 needs some means of optical correction, and it is estimated that 80 million people wear corrective lenses for which as much as $1.8 billion is spent annually. Additionally, 300,000 people a year require special corrective lenses following cataract extraction. Every year there are 9 million visits to ophthalmologists for refractive errors, accounting for 30 percent of all visits to these physicians. Additionally, there are approximately 25 million visits annually to optometrists, the majority of which are for correction of refractive errors.

The causes of corneal disease include bacterial, fungal, and viral infections; allergic reactions; improper moistening and covering of the cornea by the eyelids; birth defects; and degenerative conditions.

The incidence of legal blindness from corneal diseases, which is about 6 percent of all legal blindness, is not high in comparison to that caused by other eye disorders. Nevertheless, corneal and external eye disorders and diseases can cause monocular blindness, severe disability, and pain and require a considerable amount of physician care. Ocular infections and allergies (most of which are

conjunctival) and ocular injuries (most of which are from foreign bodies or traumatic injuries involving the cornea) are the most common eye problems.

Accomplishments

Advances in corneal disease research hold great potential for improving the ability of millions of Americans to cope with diseases and injuries of this important ocular tissue.

Corneal disease caused by bacterial infection can often be effectively treated with antibiotics. There has been some success in treating corneal disease caused by viruses. Idoxuridine (IDU), developed in the early 1960's for treating herpes simplex infection of the cornea, was the first drug proved useful for treating any human viral disease. A newly introduced antiherpes drug, vidarabine, is expected to be valuable in treating patients who either do not respond to IDU or in whom that drug produces undesirable side effects. The antifungal drug, pimaricin, whose testing was supported by the NEI, is now the drug of choice for fungal keratitis.

An important new approach to drug delivery and for treating dry eyes consists of placing ocular inserts under the eyelid where they melt, providing the eye with needed moisture or medication. Other inserts that do not melt can deliver drugs at precisely controlled rates.

When corneal diseases or injuries are not treated promptly—or despite treatment—the cornea may become scarred or opaque, thus blocking the passage of light and resulting in impaired vision or blindness. In such cases, a corneal transplant, replacement of the diseased tissue with a healthy cornea from a donor eye, may be able to restore sight. Corneal transplantation is one of the most successful of all transplant operations; its overall success rate has greatly improved over the last decade. At this time, 85 percent of all corneal transplants remain clear.

Until recently, short-lived refrigerated tissue was essential for most corneal transplant operations. Now, a choice of two procedures makes it possible to store donated corneas for a period of several days or even months or years. For short-term storage of up to seven days, a nutritive liquid called M-K media is used to keep the corneal tissue fresh and viable at a temperature of 4 degrees Centigrade. Cryopreservation, a freezing technique in which corneas can be frozen by reducing the temperature at a precisely controlled rate to minus 190 degrees Fahrenheit, is employed to preserve corneal tissue for an indefinite period of time.

Studies of the structural basis for corneal transparency have gained considerable information on how the cornea normally maintains its clarity and how injury or disease may disrupt this process. A modified specular microscope, which permits the scientist to view the endothelial cells in the intact human eye, has greatly advanced the clinical study of the growth, development, and healing of intact corneal cells.

Research on soft contact lenses has led to their use as a protective dressing or bandage which eases pain and promotes healing in a variety of corneal diseases.

Recent research into new types of contact lenses has brought about exciting new possibilities for optical correction. These may be important to the estimated 8 million people in this country already wearing either hard or soft contact lenses and will almost certainly improve the optical correction of cataract and corneal disease patients. Research to optimize optical correction and to minimize the possibility of eye damage from contact lens wear is an extremely important area for future research. Experiments with permanent-wear contact lenses are under way; the groundwork for such devices has already been laid by basic

studies. It is possible that continuous-wear lenses may one day render the wearing of eyeglasses obsolete.

Goals of Corneal Diseases Research

- Understand normal corneal development, structure, and metabolism.
- Understand how disruption of normal processes by prenatal or developmental influences, external factors, or other eye or systemic disorders can lead to corneal disease.
- Discover means to prevent corneal diseases.
- Treat these diseases effectively once they occur.
- Improve the early diagnosis of corneal diseases and classify them more accurately.
- Define with sufficient clarity those corneal diseases which are hereditary in nature in order to make rational genetic counselling possible.
- Develop effective methods of restoring visual function lost as a result of corneal diseases.

External Ocular Infections and Inflammatory Diseases

The *Corneal Diseases* Panel, in consultation with leading experts in external ocular infection and inflammation, has determined that additional research in Herpes Simplex is the highest priority within this subprogram.

Herpes Simplex

Herpes simplex keratitis, which is the most common severe ocular infection in the United States, has an estimated incidence of 297,000 annual cases. The disease typically begins during childhood or adolescence and frequently recurs, causing severe disability and major loss in productivity. It is a growing nemesis, especially among patients with primary or medically-induced immunological incompetence. Medical therapy requires frequent return visits to the physician over periods ranging from one week to several months. Approximately 50 percent of those who develop herpes simplex epithelial keratitis are likely to experience recurrence of epithelial disease or a complication of deep stromal keratitis or uveitis within two years.

The eye has served and continues to serve as the best model for studying the pathogenesis of herpes simplex infection and for developing effective methods of its prevention and cure. The antiviral drugs now being tested in the treatment of generalized herpetic viral disease were originally tested and proven in the eye. The possible therapeutic use of interferon, the mechanism of host defense, and virus latency and recurrence are best studied in the eye. Knowledge derived from such studies will provide a valuable key to understanding herpes simplex infections of the skin, central nervous system, motor nerves, and genitourinary tract, and, probably most important, to understanding the possible relationship of herpes virus to cancer of the cervix and other organs. The products of this research may thereby be of great value to other medical disciplines.

Accomplishments

Vision research scientists have made landmark advances in the study of herpes simplex and its treatment. When one considers that this virus may be a cause of cancer, these advances, which were made through the study of the virus in the eye, become even more important. The introduction of idoxuridine for the therapy of ocular herpes simplex in 1962 represented the first successful application of a drug in the control of human viral disease and stimulated extensive effort toward the development of other antiviral agents. Basic and clinical investigations have established the value of idoxuridine, vidarabine, and trifluorothymidine in treating herpes simplex epithelial keratitis, thereby reducing the morbidity of the disease and hastening the return of the patient to a normal and productive life.

Immune responses to herpes virus have been found to play a major part in the production of severe corneal stromal disease. Although the exact mechanism by which this occurs is still not known, immunosuppressive drugs, such as corticosteroids, have been used with some success to treat this condition.

Investigations have determined that the source of herpes reinfection may be the trigeminal ganglion, an aggregation of cells of the chief sensory nerve of the face, and perhaps other ganglia around the eye where the herpes virus may reside in a latent state between acute episodes of keratitis.

Research Needs and Approaches

One of the greatest research needs in this subprogram is to define the role of live herpes simplex virus, viral antigen and cell products, and the host inflammatory response in the production of secondary herpetic uveitis. There is also need to define the host factors responsible for initial acquisition of the herpes simplex virus, for expression of the primary clinical infection, and for recurrence of this disease. Emphasis should be on the genetic and immunological factors related to the variable expression of the disease. Definition of the neuronal factors responsible for viral latency and reactivation is also important. Another important research need is to develop more effective methods of treating ocular herpes simplex.

Other Important Research Areas

Herpes Zoster. Despite the low incidence and prevalence of ocular herpes zoster, this disease predominantly attacks middle-age adults, forcing loss of work and frequent, extended hospitalization. Among the elderly, dissemination of infection may lead to severe central nervous system complications and death. An animal model would facilitate research on the cause of herpes zoster. Defining the role of this virus in ocular disease and developing effective drug treatments are other important needs.

Adenovirus and Enterovirus. Adenovirus, which is the most frequent cause of epidemic ocular disease, predominantly attacks adults, resulting in significant loss of productive time, and accounts for a large number of physician office visits. Epidemic outbreaks of this disease disrupt places of work, educational institutions, and recreational units. The ocular route of infection may lead to diseases in other organs, and disseminated infection in children can produce death. Adenovirus type 12 has been shown to produce cancer in laboratory

animals, and enterovirus has caused epidemics of hemorrhagic conjunctivitis around the world. Improved techniques for early diagnosis, an animal model, and effective antiviral therapy are major research needs.

Chlamydia. Although rare in the United States, the chlamydial infection, trachoma, is a leading cause of blindness throughout the world. Recent studies have defined the differences among subgroups of chlamydia and their relationships to endemic trachoma and paratrachoma. Despite the containment of trachoma within restricted, small population groups in this country, chlamydial conjunctivitis is widespread among the young because of increasing chlamydial venereal disease which is easily spread to the eyes. Improved techniques for laboratory diagnosis and determination of the role of local immunity in this disease are important research needs.

Bacterial and Fungal Keratitis. Bacterial and fungal infections of the cornea produce several structural alterations which frequently lead to blindness. Although the incidence of bacterial and fungal keratitis is low, the morbidity of such disorders is extraordinarily high. Patients often require prolonged hospitalization and numerous physician visits over extended periods. These infections can be brought on by such causes as simple injury or contact lens abrasion. Defining the role of the host response and of microbial products in the pathogenesis of these disorders, developing more effective drug therapy, and improving drug delivery are major research needs.

Idiopathic, Peripheral, Infiltrative, and Ulcerative Keratitis. Inflammation of the peripheral cornea may result from a variety of other diseases affecting the lids, conjunctiva, general immune system, and collagen-vascular system. Inflammations such as idiopathic, peripheral, infiltrative, and ulcerative keratitis may lead to severe alteration of the corneal structure, corneal perforation, and even blindness. The possible link of these corneal problems to systemic diseases may have relevance to many areas of medicine. Research is needed to define the multiple pathways of infection.

Allergic Diseases of the Conjunctiva and Cornea. Although the incidence of visual impairment due to contact allergy and hayfever conjunctivitis is low, these entities account for a great number of physician visits and large annual health care expenditures. Vernal conjunctivitis and atopic keratoconjunctivitis may produce severely altered corneal structures and render the victim susceptible to complications of medical therapy, such as those produced by corticosteroids. These complications may be particularly devastating to the young. Major research needs include the development of effective drug therapy for these disorders as well as basic studies of pathogenesis.

Blepharokeratoconjunctivitis. Bacterial infection and sebaceous dysfunction of the lids are among the most common disorders encountered by the ophthalmologist. The frequency and chronicity of conditions such as blepharokeratoconjunctivitis account for significant annual health care expenditures. Complications of these entities include malposition of the lids, meibomitis, hordeola, chalazia, erosion of the corneal epithelium, and a variety of peripheral corneal inflammations. Research is needed to define the role of bacteria, bacterial substances, and host factors in these disorders and to examine new methods of therapy.

Dry Eyes and Tear Abnormalities, Epithelial Disorders, and Drug Delivery

Maintenance of a normal, healthy tear film/epithelium is an important

deterrent to corneal disease. Prevention of the complications of tear film/epithelium abnormalities would greatly reduce eventual surgical and hospitalization costs for these chronic, debilitating, blinding diseases and disorders. Because of this, the Panel considers this entire subprogram to be of the highest priority.

Dry Eyes and Tear Abnormalities

The tear film is that surface of the eye most directly in contact with the environment. It is critically important for protecting the eye from external influences and for maintaining the health of the underlying cornea and conjunctiva. Numerous diseases adversely affect the tear film, causing conditions that, in turn, affect the cornea. Results range from low grade chronic eye irritation to severe disease and blindness. An understanding of the basic mechanisms of tear film formation, maintenance, and breakdown is essential to controlling and curing these diseases.

Disturbances of the tear film account for irritative eye symptoms in millions of Americans and cause considerable adverse personal, social, and economic effects. Such conditions are the result of environmental factors, such as fumes, smoke, and smog; infections and inflammations; age; lid defects; poor nutrition; systemic diseases; and drugs.

Epithelial Disorders and Surface Injuries

Virtually all mechanical and chemical injuries to the eye, most ocular infections, and most damage to the eye from drying involve destruction of part of the corneal surface. Maintenance of an intact, healthy corneal surface is one of the most important requisites for normal vision. Diseases which disturb the integrity of this surface often cause decreased vision and result in pain or discomfort which is often severe enough to render the victim unable to work and which requires frequent and expensive visits for highly skilled eye care. Because such injuries and epithelial damage are so common, even modest improvements in understanding epithelial healing and the development of means of stimulating it would have considerable social and economic impact.

Drug Delivery

This is one of the most important areas in ocular care because drug delivery is an essential component of therapy. New delivery systems should be developed as a means of reducing the need for frequent instillation or application of drugs, minimizing undesirable drug interactions and side effects, reducing costs, and increasing efficiency. The way drugs affect an individual's eye can provide clues to his or her genetic make-up.

In general, there are three major methods by which drugs gain entrance to the eye. These include application in some sort of vehicle or delivery system to the surface of the eye, injection around the globe, and systemic administration.

Accomplishments

Dry Eyes and Tear Abnormalities. In the past decade, considerable advances have been made in understanding the structure and formation of the precorneal tear

film. It is generally accepted that the tear film consists of a thin lipid film at the air/tear interface, covering an aqeuous layer which contains salts, proteins, and mucin. Immediately after a blink the tear film has maximal thickness; subsequently, the thickness drastically decreases. There is evidence that biochemical changes in aqueous tear composition occur as a result of disease and environmental influences.

Epithelial Disorders and Surface Injuries. Scientists have found that many chronic epithelial defects and ulcers develop because the corneal epithelium does not adhere properly to the basement membrane. This has permitted the beginning of a rational approach to therapy. Morphological studies and scanning electron microscopy have delineated the appearance of the epithelium and some of the relationships between it and other corneal structures. However, much remains to be learned about the adhesion of the epithelium, its ability to heal and the control of such healing, the production of digestive enzymes which damage the cornea, and other factors.

Drug Delivery. Research on drug delivery and pharmacokinetics has been very fragmented. There has been a tendency for each drug or system to be tested as it becomes available under a research protocol of an individual investigator's own choosing. The results of such tests, unfortunately, cannot be compared with previous studies.

Research Needs and Approaches

Dry Eyes and Tear Abnormalities. Because many hours of productivity are lost due to ineffective treatment of common eye irritations, especially dry eyes in the aged and those irritations suffered by contact lens wearers, much greater attention should be placed on preventing the more serious consequences of these conditions, rather than on treating them once they occur. It is imperative, therefore, that studies of new and old drugs be continued or initiated in order to provide information that can facilitate therapy and reduce side effects.

Epithelial Disorders and Surface Injuries. Prevention and treatment of longstanding epithelial defects are important priorities because the stroma frequently ulcerates and sometimes perforates within the defect. In terms of visual impairment, disability, and cost, this area of research deserves top priority. The problem should probably be approached by attempting to understand how the epithelium adheres to its underlying tissue and by attempting to find epithelial growth stimulators. Improved soft contact lenses may also be helpful.

The intact but inflamed epithelium still causes considerable discomfort and reduction of vision. Eyes that have had chemical burns, serious infections, or that suffer from dryness are in this category. Such conditions are frequently bilateral and often afflict young people—two reasons which make their cost in human misery so high. It is very important to find ways to ameliorate these conditions and to prevent them from causing stromal opacity and vascularization.

Drug Delivery. There is great need to evaluate thoroughly the efficacy and applicability of the various available methods of drug delivery. Measurements should be made of the drug's bioavailability-penetration rate, duration, and metabolic breakdown. Biochemical tests should include direct analyses and the study of factors involved in the variability of drug response in humans as well as laboratory animals.

Refractive Problems and Contact Lenses

The Panel has selected Continuous-Wear Contact Lenses, New Contact Lens Materials, and Orthokeratology as the research areas of highest priority within this subprogram.

Nearly 94 million people in the United States wear eyeglasses or contact lenses to improve their vision. Most of these people have refractive errors: nearsightedness (myopia), farsightedness (hyperopia), astigmatism, and other conditions. Usually, refractive errors are not serious and can be easily corrected with prescription lenses.

The annual cost of visits to ophthalmologists and other physicians for refractive errors is estimated to be $150 million annually. The cost of optometrists' services and materials per year is almost $1.2 billion, of which the greatest portion is for the correction of refractive errors.

When light enters the normal eye, it is refracted or bent by the cornea and by the lens. These tissues bring the light to a single, sharp focus on the retina, the light-sensitive tissue at the back of the eye. Here, light impulses are converted to nerve impulses and are transmitted to the brain where they are interpreted and vision takes place.

In the normal eye, clear vision depends upon the existence of a precise relationship between two eye measurements: the refractive power of the cornea and lens and the length of the eye. Any variation in this relationship results in a blurred image or refractive error. The cause of this variation is usually unknown, but both environmental and genetic factors may contribute to the development of refractive errors.

Continuous-Wear Contact Lenses

Those wearing contact lenses can be divided into two categories. The largest group, perhaps 7 million people in the United States, wears contact lenses as an alternative to correction by eyeglasses. The second group, which numbers about 1 million people, requires contact lenses because of pathological conditions of the cornea or to provide better vision following surgical removal of cataract. It is this latter group for which continuous-wear contact lenses would be most beneficial since a large portion of these people have great difficulty in manipulating contact lenses or are simply unable to handle them at all. In addition, many pathological conditions of the cornea require that the lenses be worn continuously during sleep as part of the therapeutic process. Finally, the potential use of a continuous-wear soft lens as a mode of drug delivery to the eye has just begun to be explored.

New Contact Lens Materials

Many new polymers have been developed and are undergoing experimentation for possible use as contact lens materials. There is great potential for materials with properties superior to those in use today, particularly with regard to gas permeability, wetability, surface quality, optical quality, durability, and stability.

Orthokeratology

Orthokeratology consists of fitting a series of specially designed, slightly

flattened contact lenses which gradually remold the cornea. There have been numerous studies and publications concerning the effects of contact lenses on corneal integrity, curvature, topography, and changes in the refractive error of the eye. The causes and mechanisms for these alterations are either not known or not agreed upon by ophthalmic scientists. Advocates of this technique claim to make constructive use of the above changes without sacrificing corneal or ocular integrity or vision. The exact degree of benefit and the risks involved remain to be defined scientifically.

Accomplishments

Continuous-Wear Contact Lenses. For most people with refractive errors, corrective eyeglasses or contact lenses provide simple and highly satisfactory restoration of clear, sharp vision. In recent years, the introduction of hydrophilic, flexible, soft contact lenses has broadened opportunities for treatment of refractive errors, making it possible to correct irregular corneal surfaces which previously had been extremely difficult or impossible to treat. They have also made it possible to provide comfort, protection, and useful vision shortly after corneal transplant surgery, in the presence of bullous keratopathy, or in certain very debilitative dry eye syndromes. Also, soft lenses enormously simplify the refractive correction of the newborn and young, and they provide a means of correction for many who are unable to wear hard contact lenses.

New Contact Lens Materials. The development of new contact lens materials has dramatically changed this field. Soft contact lenses can permit instant, comfortable wear for prolonged periods of time. Newer materials which permit greater oxygen permeability are under study for use in contact lenses which may be worn continuously without damaging the cornea.

At present, a few practitioners are experimenting with having their patients wear soft hydrogel contact lenses continuously. They have experienced mixed results, and the reason why such variability in response occurs should be investigated. Still, continuous-wear soft contact lenses can be looked upon as a realistic goal that can be achieved in a relatively short time.

Polymethylmethacrylate (hard) contact lenses have been used successfully by millions of people for years. Many others have discontinued or have not been able to wear them due to a variety of reasons, including intolerance, optical problems, and improper handling. Nevertheless, this type of lens is still the contact lens of choice for many refractive conditions such as high astigmatism, corneal distortion, and other cases where hydrogel lenses are not suitable.

Orthokeratology. Some practitioners, primarily optometrists, believe they have demonstrated that orthokeratology can reduce myopia and in some cases permit visual correction without the need for glasses. More precise studies are needed of the risks involved, changes in corneal shape, maximal degree of correction, and duration of such correction. Such prospective studies should be able to remove the controversy from this promising field and provide objective data for evaluation of safety and usefulness.

Research Needs and Approaches

Continuous-Wear Contact Lenses. Hydrogel lenses have been available to the general public since 1971. The current state of the art indicates a need for further refinements in both the refractive and therapeutic uses of these lenses and for their further development as vehicles for drug delivery.

The evolution of soft contact lenses is hampered by a lack of instrumentation for measuring physical parameters, the composition of lens materials, the state of manufacturing technology, and by the absence of a detailed study on the effects of such lenses on corneal metabolism and physiology.

The effects upon corneal physiology of new soft lenses intended for continuous-wear need to be assessed qualitatively. The causes of superficial vascularization, which occurs in certain patients who have worn such lenses for extended periods of time, have to be defined. Criteria for the safety of each new type of lens material must be established. Studies should weigh any possible loss of vision against the advantages of these lenses: extended wear, comfort, and other factors.

At present, because continuous-wear contact lenses are not available for other than investigational use, the surgical treatment of cataract often involves the insertion of a plastic lens within the eye. A continuous-wear contact lens could serve as an alternative to the intraocular lens, contributing not only to greater safety, but to greater flexibility in changing the refractive correction, should that need arise.

New Contact Lens Materials. Responsibility for the development of new lens materials and for setting standards for their safety is now mostly borne by manufacturers. However, determining the properties required for maintaining normal physiology and establishing standards for clarity, surface quality, and durability must be the responsibility of the scientific community. In addition, scientists must determine the guidelines for quality and the limits within which there can be acceptable trade-offs.

Both short-term and long-term benefits can be realized. Guidelines written by scientists which determine the quality of lenses and their desired properties can act as an impetus to more rapid development of better materials, thereby affording the patient the earliest possible benefit without undue suffering or risks.

Orthokeratology. Because of their purely clinical approach, previous studies in orthokeratology have been limited by inadequate controls. Although there have been a few quantifiable studies, new, impartial, carefully controlled clinical trials are required to determine how well orthokeratology can correct refractive errors, the duration of correction, and the complications and risks involved.

Other Important Research Areas

Corneal Physiology. Contact lenses, hard and soft, now represent a considerable portion of refractive corrective prescriptions. They are frequently the only acceptable corrective form available to minimize the optical problems of the individual who has had one cataract removed, to "resurface" optically the irregular cornea, to provide mechanical protection for the cornea with bullous keratopathy, and to treat many other pathological conditions. However, neither the short- nor long-term effect of hard and soft contact lenses on the physiology of healthy or diseased corneas has been fully defined. Studies in this area are needed.

Keratoconus. Keratoconus is a noninflammatory, progressive, chronic deformity of the central portion of the cornea. It is characterized by corneal protrusion and thinning and varies in degree from a mild form, which can be corrected with glasses, to a more advanced form, which is commonly corrected with contact lenses. Patients who progress beyond the stage where contact lenses may be worn usually receive a corneal transplant (keratoplasty). Thermokeratoplasty, a

new therapy employing the controlled use of heat to reshape the cornea with keratoconus, needs to be standardized and carefully evaluated in a controlled study in comparison with corneal transplantation.

Astigmatism and Corneal Distortions. Eyeglass correction of astigmatism, particularly after cataract surgery, is rarely an important problem. However, adequate visual restoration in the aphakic patient with any type of contact lens, but particularly with continuous-wear soft contact lenses, represents a serious problem. Corneal astigmatism resulting from penetrating keratoplasty is the most frequent disabling complication of this procedure and the most difficult to manage successfully. It almost always affects the binocularity and productivity of the affected patient. Research needs include studies of the factors involved in corneal image distortion and in surgically induced astigmatism. Measures for preventing or reducing the magnitude of postoperative astigmatism should be developed.

Corneal Edema, Dystrophies, and Inherited Disorders

The Panel determined Endothelial Morphology and Function In Vivo to be of highest priority within this subprogram.

The fragile endothelial layer which lines the inside of the cornea is critically important in maintaining proper hydration of the tissue. Endothelial failure leads to corneal edema which results in decreased corneal transparency, poor vision, and often severe pain. Many older people suffer from a spontaneous deterioration of the corneal endothelium, a condition known as Fuchs' dystrophy. Unfortunately, this disease usually affects both eyes and often causes blindness.

Endothelial Morphology and Function In Vivo

Injury to the endothelium may occur inadvertently during intraocular surgery, such as for cataract, or be the result of chemical or mechanical injury. Endothelial cell destruction from ocular disease is also not uncommon. Long-term treatment with certain drugs is also suspected as a cause of injury to the endothelium, particularly when its function is already compromised by age. Abnormal systemic conditions can probably influence the health of the corneal endothelium, although virtually nothing is known about this. Fuchs' dystrophy, the most common endothelial degeneration with aging, for example, occurs about three times more commonly in women than in men and may be influenced by the general effects of hormonal changes in aging.

Because endothelial dysfunction is usually permanent, corneal transplantation may provide the only hope for restoration of vision. Success of the corneal graft depends, in turn, on the adequate function of its endothelial layer.

In particular, it should be noted that Fuchs' and other dystrophies of the cornea are probably examples of the general aging process in other organs of the body. Understanding the normal function of the endothelium and connective tissue of the cornea and how they are degraded by these dystrophies may lead to insights into general human aging.

Accomplishments

Research with animals, in particular, rabbits, has provided a great deal of valuable knowledge about the function of the endothelium, both as a fluid barrier

and as a metabolic pump. However, the human endothelium is unique in certain ways: for example, its inability to regenerate and its susceptibility to certain dystrophic changes limit the applicability of findings from animal studies of the corneal endothelium to human eye disease. Studies in humans are therefore necessary.

Research Needs and Approaches

Improvements in the design and instrumentation of clinical endothelial examination techniques such as specular microscopy and fluorophotometry should be encouraged. Additional knowledge of endothelial regenerative capacity, the endothelial effects of intraocular surgery, and the characteristics of endothelial diseases is needed. An attempt should be made to estimate more accurately the capacity of individual corneal endothelia to withstand different intraocular surgical procedures. Scientists need to understand the relationship between endothelial cell population density and the capacity of the cornea for healing.

Observations of the endothelial effects of various drugs and of different methods of corneal preservation upon the endothelium of transplants have potential for immediate application. The irrigating solutions now used in vitrectomy operations have become increasingly important because such procedures may produce corneal edema. There are data which suggest the need for irrigating solutions which minimize endothelial damage. Long-term studies of endothelial healing, the development of endothelial dystrophies, and the effects of chronic drug administration upon the endothelium have significant potential for payoff.

Long-term studies of the possible cellular repopulation of the endothelium as an alternative to keratoplasty should be encouraged. If success is achieved in the rabbit, extension to primate models should be initiated and then, finally, trials in humans should be undertaken. The collection of sufficient human endothelial cells for culturing and clinical testing may require the cooperation of more than one center.

Another Important Research Area

Corneal Dystrophies and Inherited Disorders. Corneal dystrophies can be divided into those problems concerned with development and those related to aging. Although they are not a major cause of blindness, they can cause considerable discomfort and inconvenience to those afflicted by them. Because of their high prevalence, they are of substantial social and economic importance.

A significant number of corneal disorders are caused by untoward genetic or environmental influences. In rare cases, affected individuals are blind from birth with tragic consequences for themselves and their families. More frequently, hardship is caused by partial disablement and the need for continuing medical care.

The ametropias, a very large group of visual disorders which are influenced by genetic or environmental factors, are also important. These range in severity from inconvenient, small refractive errors which are correctable with eyeglasses or contact lenses to malignant myopia that can ultimately result in blindness.

In addition, exogenous insults need to be considered. Climate, for example, appears in some obscure way to be able to cause severe, bilateral blinding deterioration of corneal tissues as in actinic or climatic keratopathy. Pterygium, a

very prevalent condition, also appears to be related to climatic factors, as do benign and malignant squamous neoplasms of the conjunctiva and cornea.

Major research needs in this area include tissue culture study of the synthesis of collagen and polysaccharides by corneal cells and how this process is modified in genetic disorders, developmental studies in the mammalian cornea, study of aging and stress on the endothelium and on Descemet's membrane, and classical genetic studies of myopia and hereditary corneal disorders.

Corneal Transplantation and Stromal Injury and Repair

Research in this entire subprogram is considered by the Panel to be of the highest priority.

Corneal Transplantation

Approximately 10,000 corneal transplants are performed each year in the United States. This is an operation which can visually rehabilitate those who are blind from corneal disease. Often, those afflicted are young, sometimes only infants. Increasing the potential social and economic savings afforded by this procedure is surely worth a relatively modest research investment.

In addition to the beneficial effects of corneal transplantation, the cornea represents a somewhat simplified anatomical system of significant importance to general medicine, particularly with respect to immunological study. It provides an ideal study model because there are no blood vessels in the cornea, it is accessible to sampling and therapeutic agents, and the second eye can be used as a control. The corneal stroma is relatively acellular, and it is easy for immunological reactions to be studied on a single cell basis and for graft reactions to be quantified. Thus, corneal transplants are an ideal structure for studying, for example, tissue typing.

For these and other reasons, the study of corneal transplantation may well provide information of great benefit to the general field of tissue and organ transplantation. The relatively milder reaction of the body to corneal transplantation may help in identifying possibilities for therapy which are overlooked during massive reactions to kidney or heart transplants.

Stromal Injury and Repair

As all major infections and chemical and mechanical trauma of the cornea heal, opacities which impair vision are produced. Trauma, especially in children, often causes serious visual impairment which leads to significant social and economic problems for the child and his family. A long-term objective of research in this area is to modify the healing process to produce a less opaque and mechanically stronger tissue. Studies of healing in the cornea are relevant to the healing of other tissues and therefore have potentially important value in other areas of medicine.

Accomplishments

Corneal Transplantation. One of the primary reasons this Panel chose corneal transplantation as a priority area for NEI-supported research is that recent progress has been rapid and that further progress can be expected with a small

investment of funds and manpower. Findings in this area can serve as an important model and source of information to the transplant field as a whole.

The specular microscope now enables scientists to examine corneal tissue more thoroughly before it is used as a graft. This procedure, as it is now developing, may greatly increase the success of corneal grafts by reducing the amount of primary tissue failure. However, further developmental work is necessary.

Eye banking has involved taking the donor eye after death and simply putting it in a refrigerator. Placing the corneal tissue which is to be used for transplantation in a nutritive medium (M-K media)—a recent accomplishment—has revolutionized corneal transplantation. It also appears to have dramatically decreased the number of primary tissue failures and permitted the storage of corneal tissue for a longer period of time. As a result, surgeon, recipient, and optimal tissue can now be brought together as needed. Work on corneal cryopreservation and tissue culture promises even longer storage of tissue. This will facilitate tissue typing and other kinds of tissue matching. M-K media preservation and, to a lesser extent, cryopreservation are now in general use by many eye banks.

Two very promising approaches have been developed for the improved prevention of corneal graft rejection, a particular problem in treating cases of chemical burns and badly vascularized corneas. One involves simply dipping the donor cornea in blocking antibody, a technique that has been used successfully in animals. The other involves cross-matching the tissue by HLA antigen type. Preliminary studies have shown that those who are antigenically compatible seem to be less susceptible to graft rejection.

Stromal Injury and Repair. The prospects of understanding, and of possibly controlling, the physical, chemical, and biological factors that cause the development of a weak, opaque cornea have been considerably increased by recent research developments. If healing could take place without opacification, much blindness could be prevented. Recent studies using the eye as a model have also demonstrated that tumors produce an angiogenesis factor which stimulates the formation of blood vessels in normal hosts. Furthermore, extracts of cartilage and other substances prevent this ingrowth of vessels. The possibility of preventing vessel ingrowth has profound implications in the eye for the treatment of diabetic retinopathy, for the prevention of corneal vascularization after injury, and, of course, as a model for vascularization and tumor growth elsewhere in the body. Studies of the molecular basis of corneal scarring hold promise that, once understood, this process can be blocked and normal healing promoted. New technological developments in tissue preparation, cell culturing techniques, and methods for studying macromolecules should facilitate such investigations.

Research Needs and Approaches

Corneal Transplantation. Specular microscopy needs to be developed into a simple and convenient procedure so that eye banks can routinely examine tissue to be certain that corneal cells, especially endothelial cells, are in optimal condition for corneal transplantation. This would include making sure not only that the cells are undamaged, but that there are an adequate number of residual endothelial cells on the donor tissue.

The handling of corneal donor tissue can be facilitated by improving the present M-K storage medium and adapting knowledge gained through tissue culture to improved corneal storage. Ideally, a method could be developed which

requires little care and involves no great hazard to the tissue but which permits some metabolic function to take place in the corneal tissue.

A trial of blocking antibody in human corneal transplantation should be undertaken. In addition, the potential value of HLA typing and HLA cross-matching in reducing the rate of graft rejection should be further investigated.

Stromal Injury and Repair. There is need for biochemical and ultrastructural characterization of the normal and scarred cornea. Most important, pharmacological manipulation of corneal metabolism as a means to avoid or reverse scarring during healing should be investigated.

Tumors and Other Lid, Conjunctival, and Orbital Problems

Although this area has been relatively neglected, and some additional effort would be worthwhile, advances in this field are likely to result primarily from research in biomedical fields other than vision. For this reason, the Panel has not identified this subprogram for priority emphasis.

Pseudotumors and Lymphoma. Pseudotumors are a loosely defined but clinically important group of orbital inflammatory disorders. They occur without readily apparent cause and can create considerable visual morbidity. In general, little is gained by surgical intervention except for the establishment of a tissue diagnosis when the presence of a true neoplasm cannot be ruled out by other means. Not only does pseudotumor pose a diagnostic problem for the physician, but the pathologist also faces a dilemma in certain cases in distinguishing a pseudotumor from a true lymphoma with systemic and possibly lethal implications. Improved diagnostic methods are therefore needed which will render biopsy unnecessary as well as natural history studies to determine whether pseudotumors ever evolve into lymphoma and whether the latter tumors ever metastasize from the orbit to other sites in the body.

Tumors of the Lids—Basal Cell Carcinomas. Basal cell carcinomas are the most common cancer of the eyelid, the site of 80 percent of all facial cell tumors. Basal cell tumors at the nasal junction of the eyelids also present special problems in management. Because basal cell carcinoma of the lid is related to exposure to sunlight as well as to race, it represents an interesting model of an environmentally induced tumor with a genetically determined component. Epidemiologic studies in this area are therefore warranted.

Malignant Melanoma. Malignant melanoma arising from acquired melanosis of the conjunctiva is a particularly important ophthalmic condition. In the past ten years or so, the treatment for this condition has undergone change from wide extirpative surgery to local resection. While not a common lesion, it is one which has distinctive characteristics. Study of its features may lead to better understanding of its nature and serve as a firm basis for therapy.

Orbital Tumors. Pathological processes that involve the orbit may arise either from soft tissues within the orbit itself or by invasion of the orbit from an adjacent cranial depression or sinus. As a result, the globe may be pushed forward, and the function of the optic nerve, extraocular muscles, and globe may be disturbed. Improved diagnostic measures, possibly making use of fiberoptic probes for direct visualization of the tumor and surrounding tissues and structures, could save many patients from extended hospitalizations and surgery.

Cataract

Introduction

A cataract is an opacity or group of opacities in the crystalline lens of the eye, which interferes with the passage of light to the retina, thereby causing visual impairment. The major types of cataract are:

- *senile or degenerative cataract,* in elderly people
- *traumatic cataract,* resulting from injury
- *drug-induced cataract,* from the toxic effects of drugs used to treat ocular or systemic disorders
- *radiation cataract,* from the harmful effects of environmental or therapeutic radiation
- *congenital and/or genetic cataract,* defects present at birth or developing soon afterward
- *secondary cataract,* from complications of other eye diseases, conditions, or injuries

The only way of treating most cataracts is to remove them surgically. The patient must subsequently be fitted with glasses or contact lenses, or a plastic lens implant at the time of surgery.

In an effort to determine the causes of cataract and hasten the day when medical treatment can be used effectively to treat or prevent cataract, the NEI supports investigators who study the normal lens and natural and experimental cataracts. These scientists are seeking clues to the origin, mechanisms of formation, and improved treatment of this disease.

The *Cataract* Panel recommends that the National Eye Institute's program of research in this field be divided into the following subprograms:

1. The Normal Lens
2. Senile or Degenerative Cataract
3. Diabetic Cataract
4. Congenital, Metabolic, and Genetic Cataracts
5. Cataract Induced by Drugs and Radiation and Occurring Secondary to Other Eye Disorders
6. Dislocated Lens
7. Accommodation and Optical Problems of Cataracts and Aphakia

This new categorization reflects the breadth of knowledge and scope of concern of cataract research.

Importance

Cataract accounts for approximately one-sixth of all cases of visual impairment in this country. Even though there are approximately 300,000 operations to remove cataract each year, there are still an estimated 1,670,000 Americans who have difficulty seeing with one or both eyes, even when wearing glasses, because

of developing cataract. Of these, about 183,000 Americans six years of age or older are unable to read newspaper print because of unoperated cataract, and of these, 64,000 Americans are totally blind—10,000 since birth—because of cataract.

During 1972, there were 283,000 discharges from short-stay hospitals for which cataract was the main diagnosis, roughly more than one-half of all hospitalizations caused by eye disorders. From April 1973 to April 1974, cataracts accounted for 2,723,000 visits to physicians. Clearly, in terms of physical disability, suffering, and financial burden, cataract constitutes a serious health problem.

Accomplishments

During the past ten years, NEI-supported investigators have been able to clarify how cataract is caused by diabetes, galactosemia (a rare genetic metabolic disorders), uveitis (an inflammatory disease of the eye—see the *Retinal and Choroidal Diseases* report), German measles, and other diseases. Many cataracts of previously unknown origin are now known to result from inherited or prenatal chromosomal abnormalities.

Investigators have also clarified how drugs administered to treat other conditions can cause cataract, leading to their more careful use.

A great deal has been learned about the normal lens and how it develops and maintains its transparency.

New and improved techniques for cataract removal have been developed; one involves breaking up the cataract by means of an ultrasonic probe and removing the lens material through suction. The value of these newer methods is still being compared with traditional procedures for cataract removal.

New methods for providing optical correction of vision following cataract surgery have been developed. Surgical implantation of a plastic lens inside the eye is being used in certain patients and various types of continuous-wear contact lenses are being tested.

Goals of Cataract Research

Cataract extraction is one of the most successful of all major surgical procedures. Although NIH-supported research has contributed significantly to the advancement and perfection of modern surgical techniques, support for some of the most recent developments in cataract extraction has come almost exclusively from cataract surgeons themselves and from organizations in the private sector. Because of economic incentives, it is certain that industry will continue to support research and development in this area. For this reason, the National Advisory Eye Council recommends that the National Eye Institute continue to place primary emphasis on supporting research on the prevention of this disease. The NEI should, however, be very concerned with the safety and efficacy of new surgical techniques as they are developed and take the lead in encouraging, organizing, and/or sponsoring clinical trials and other types of applied evaluative research at the appropriate state in their development.

In view of the foregoing, the major goals of the NEI *Cataract* research program are to:

- Determine the causes of cataracts.
- Find means of preventing or slowing cataract development.

- Prevent development of amblyopia in children with cataract.
- Devise new methods for correcting optical problems that follow cataract surgery.
- Evaluate the safety and efficacy of new methods of cataract extraction.
- Improve the quality of life and adaptation to new spatial relationships of patients who have undergone cataract surgery.

The Normal Lens

The major attribute of the lens, its transparency, depends for its development and maintenance on the precise interaction of a number of physical and chemical factors. Gathering information on lens differentiation, growth, and metabolism, on how the molecular structure of the normal lens is preserved, and how disruption in these processes causes cataract formation requires the search for and application of new research technology.

Information gained from these basic investigations, especially in laboratory animals, is already being applied to the study of the human lens and of senile cataract.

Accomplishments

Transport. As a result of animal studies conducted by NEI-supported researchers, it is now known that with aging the ability of the lens to accumulate amino acids, essential for protein synthesis, is decreased. However, the cause of this is not known.

An interesting recent development is the implication of glutathione in the transport of amino acids and cations into the lens. Loss of glutathione may be a factor in the accumulation of sodium and loss of potassium which contributes to the formation of various kinds of cataract. Since glutathione is present in most cell membranes, this finding may have general significance for biomedical research and needs to be studied further.

Protein Chemistry. Considerable progress has been made in understanding lens proteins. The lens is composed of three major groups of soluble proteins—alpha, beta, and gamma crystallin—and an insoluble protein fraction. The primary structure of certain of these proteins has been worked out and others are under investigation. The impact of aging on alpha crystallin is now partially understood, and attention has turned to the effect of such changes upon the physical state of the protein and on the development of the cataract.

Research on bovine alpha crystallin has shown that with aging there is a shift from low molecular weight types to giant macromolecules. It is clear that such components can act as light scattering points and, when present in sufficient concentrations, cause cataract.

The situation in the human lens is similar, although not fully understood at present. Recently, methods have been developed for direct measurement of the size of the protein macromolecules in the intact human lens. Further study of the mechanism by which the large molecules are formed in the human lens is needed.

Lens Embryology. Congenital cataracts can arise from genetic abnormalities. Genetic defects can also cause absence of the lens and anomalies of lens shape, size, or position. For an understanding of these pathological conditions, a

thorough knowledge of normal development is essential. Because of practical considerations, studies on human embryonic lenses are not commonplace, and animal models must be used.

Considerable progress has been made during the past decade in understanding lens development. Despite these findings, which need further expansion, many aspects of lens development and formation are still poorly understood.

Work of this nature can be expected to increase understanding of lens formation, which in turn may have implications far beyond the field of lens embryology and serve to expand general knowledge of embryonic differentiation.

Molecular Biology. It has been shown in the past decade that the specific proteins of the lens, the crystallins, do not appear until lens formation is well underway and that their manufacture is unique for the lens cells. At the genetic level, this means that lens differentiation is now considered to involve the turning on of specific genes. Recently developed techniques have made it possible to bring these investigations one step closer to identifying the actual gene involved. The very potent tools of modern molecular biology, utilized in combination with experimental embryology techniques, make possible expanded studies of lens cell differentiation. They offer the exciting promise of better understanding of the control of individual gene activity.

Research Needs and Approaches

- Definition of transport mechanisms of electrolytes, carbohydrates, amino acids, and lipid molecules in normal human and animal lenses.
- Determination of the chemical composition and metabolism of proteins, lipids, and carbohydrates in normal human and animal lenses.
- Control of enzymatic pathways for synthesis and degradation of proteins, lipids, and carbohydrates.
- Culture of the normal human lens.
- Characterization of the morphological organization of the lens epithelium, lens fibers, and zonules by electron microscopy.
- Determination of the electrical gradients of the entire lens and electrical potentials of individual lens fibers.
- Definition of the synthesis of macromolecules and lens fiber differentiation in the embryonic lens.
- Investigation of the function of intracellular lens organelles by electron histochemistry.

Senile or Degenerative Cataract

Lens opacities develop in the majority of elderly people. Their incidence increases progressively after age 50 and approaches approximately 95 percent of the total population at age 85 or older.

The rate of development and particular type of senile cataract varies considerably with the individual. In most cases, senile cataracts can be successfully removed surgically and useful vision restored through various means of optical rehabilitation. In the United States, over 300,000 cataract operations are performed annually.

Accomplishments

Classification. Recent developments in objectifying the classification of cataract may provide the necessary tools for long-term documentation and statistical evaluation of the stages of senile cataract progression in entire populations. Thus the natural history of the disease may be clarified. Optical equipment for photography and precise measurement of the size and density of cataract has been developed. This provides permanent documentation of each opacity, which can later be compared and properly classified by independent observers.

Such techniques will make possible correlations of the appearance of cataracts in various stages of development with subsequent laboratory studies once they have been removed. Furthermore, photographic documentation would be valuable for long-term study of the effects of environmental or nutritional factors on cataract formation.

Causes and Pathogenesis. Senile cataracts develop during a span of three to twenty years. Their causes are unknown, but during aging a series of metabolic changes are known to occur in the lens and in the surrounding fluids which may contribute to cataract formation. Environmental factors such as ultraviolet light may have a cumulative effect on the lens which eventually results in cataract formation; however, this has not been proved. During the last few years, NEI-supported investigators have begun to gather information needed to determine which types of changes occur in the lens during senile cataract formation. These studies have shown that in senile cataracts there are abnormalities in lens proteins, lens membranes and their lipids, lens transport of electrolytes, and in advanced cataracts, lens hydration.

Abnormalities in Lens Proteins. Proteins account for 33 percent of the weight of the normal human lens. Thus, the lens contains a higher percentage of protein than any other body tissue. Proteins, which are found inside the lens fibers, are arranged in such a way as to allow the passage of light through the lens. Small proteins in the lens can aggregate and become larger ones. It has been suggested that proteins of high molecular weight can scatter light and thus contribute to lens opacification. High molecular weight proteins have in fact been found in human senile cataract.

Chemical dissection of lens protein can be performed by agents which split the bonds between protein molecules and between proteins and lipid molecules in lens fiber membranes. Studies of the proteins of the normal human lens and of senile cataract have yielded the following observations:

1. In senile cataract, the concentration of proteins which have strong chemical bonds is higher than that found in the normal senile lens. Strengthening of chemical bonds can result from changes in amino acid sequence or composition. Thus, investigators have turned their attention to the structure of cataract proteins, searching for abnormal patterns of organization, orientation, or amino acid sequence.

2. Aggregation of lens protein is abnormal in human senile cataract.

3. In the normal lens, the breakdown of protein is slow and regulated by specific enzymes. However, in senile cataract this process appears to be accelerated for reasons which are not yet known.

Lens Membranes and Their Lipids, Lens Transport of Electrolytes, and Lens Dehydration. The water content of the lens is extremely low. This state of relative dehydration maintains the lens transparency. When present in excess, water can cause cataract by forming vacuoles and water clefts which scatter light and decrease

vision. Thus, among other things, cataract prevention depends upon the perfect functioning of lens water extrusion mechanisms. In the normal lens, the preservation of lens dehydration results from pumping sodium ions from the lens. Lens cell membranes are made of various types of lipids, and modifications of their chemical composition affect the extrusion of sodium and water by the lens. Studies of these lipids in human senile cataract have yielded the following observations:

1. The chemical composition of lens membranes is abnormal in human senile cataract. Analyses have shown that cholesterol and other types of lipids are increased and their fatty acid content changed in senile cataract as compared with normal lenses.

2. The sodium content is increased and sodium-potassium-ATPase activity may be depressed in human senile cataract.

Treatment. At present there is no medical treatment for senile cataract. Once the basic mechanisms which lead to cataract formation are identified, a scientific approach to therapeutic development can follow.

The development of safe and effective methods for extracting senile cataracts is one of the great achievements of modern medicine. Once accepted as a natural consequence of aging, senile cataract is today recognized as a disease which can usually be successfully treated, resulting in the satisfactory restoration of vision. Thanks to improved microsurgical techniques developed through research, cataract patients today are able to leave the hospital within a few days following surgery.

Following cataract extraction, the optical function of the natural lens must be provided by an artificial substitute such as eyeglasses or contact lenses. In the majority of patients, successful optical correction is achieved; however, a small number of patients are bothered by distortions in the size or type of images with both glasses and contact lenses.

The development of new methods of cataract extraction, including ultrasonic liquefaction of the lens and its removal by suction through a hollow needle, and intraocular plastic lens implantation have been of great interest to both physicians and their patients. However, widespread publicity has tended to overglamorize these techniques, stressing their technological aspects and their potential benefits, while playing down their possible risks or contraindications.

There are many optical advantages to intraocular lenses because they replace the extracted natural lens in practically the same location. Thus, the visual orientation of patients who have had an intraocular lens implanted can be excellent. However, certain complications of cataract surgery, such as swelling of the cornea or macula, may appear more frequently in those who have received an intraocular lens implant.

Approximately 10,000 to 20,000 intraocular lenses will be implanted in the United States in the coming year. The Food and Drug Administration has recently established guidelines to regulate the use of this device. However, lack of controlled clinical trials and uncertainty of the long-term results of implantation make it difficult to assess whether the ultimate benefits of this procedure outweigh the risks. Thus, a well-controlled study of the safety, tolerance, and efficacy of intraocular lenses in humans is needed.

Research Needs and Approaches

- Culture of human senile cataract in test tubes.

- Determination of electrolyte, protein, sugar, and lipid composition and morphological abnormalities in various types of senile cataract as compared to age-, sex-, and race-matched normal human lenses through the use of new biochemical and biophysical techniques.
- Classification of human senile cataracts after documentation of structural abnormalities by photography, television, and other electronic means.
- Comparison of chemical abnormalities in experimental animal cataracts with those of human senile cataracts.

Appendix: Epidemiology of Senile Cataract

Epidemiology is a quantitative, analytical discipline broadly concerned with the study of disease in groups of people. It is an approach well-suited to assessing the magnitude of a problem, identifying possible causative factors, and determining the safety and efficiency of new therapeutic techniques.

The many conditions known to cause cataract account for only a small portion of the total problem. As yet, there is no convincing explanation for the large group classified as senile cataract which unfortunately has received little epidemiologic attention in the past.

Accomplishments

The limited studies done to date have provided some promising leads. Investigators have demonstrated an inverse relationship between altitude and cataract prevalence in the Punjab, India, despite the fact that potential exposure to ultraviolet light, a presumed risk, would be greater at high altitudes. This suggests that genetic or other environmental factors are of greater importance. However, dietary factors such as the mineral content of drinking water, quality and amount of food intake, and/or socioeconomic status could play a role in cataract formation in India.

In the United States, by adding ocular examinations to an ongoing comprehensive study of the incidence of cardiovascular and other diseases in a defined population in Framingham, Massachusetts, investigators under contract to the National Eye Institute have tapped a rich source of information at relative little cost and effort. Preliminary analysis of their results indicates that total serum phospholipids are higher in members of the study population with senile cataract. If these findings are confirmed, they will provide an important "chemical handle" on senile cataract and stimulate further epidemiologic studies in other aging populations.

Research Needs and Approaches

Two different aspects of the problem require measurement:

1. The incidence of cataract responsible for significant reduction in visual acuity. This represents the greatest impact on society in terms of visual disability, need for health care, and economic and social cost.
2. The number of cataracts resulting in irreversible blindness, either from complications of advanced untreated cataracts (e.g. secondary glaucoma) or from complications of surgery.

A number of methods exist for acquiring the data; however, none is entirely satisfactory:

1. *Number of operations performed.* Theoretically, this reflects the incidence of cataract and is a measure of the practical totality of the problem. Unfortunately, it depends as much on the availability of surgeons, indications for surgery, and the patient's awareness of the problem as it does on the number and severity of cataracts in the community. Hence, this method still understates the problem to a significant degree.
2. *Blindness registries.* These should provide valid estimates of those blinded by cataract; however, an unknown number of those individuals have surgically correctable disease. To be useful the system must distinguish between the two classes of blindness.
3. *Prevalence surveys.* Combined with good operative data, prevalence surveys are the most direct means of acquiring the information needed. However, the cost is enormous and standardization is extremely difficult. The best data available have been generated in the aforementioned Framingham Study. Forty-six percent of those age 75 to 85 had cataracts which reduced their visual acuity to 20/30 or less.

Diabetic Cataract

Ten to fifteen percent of patients admitted for senile cataract surgery in the United States and England have overt diabetes mellitus or abnormalities in blood sugar levels. Thus, it is possible that diabetes mellitus may contribute to the development of senile cataracts that require surgical removal. Cataract can also add to the visual loss and difficulties of people with diabetic retinopathy.

Accomplishments

Through research supported by NEI, the way in which diabetic cataract develops is now well understood. Excess glucose in the lens is converted into sorbitol, a sugar alcohol that accumulates in the lens and draws in water which damages the lens fibers, leading to cataract. The conversion of glucose to sorbitol is triggered by the enzyme aldose reductase.

Several drugs and chemicals have been shown capable of inhibiting the action of aldose reductase in the lenses of laboratory animals. Such studies may lead to the development of drugs which can delay or slow the formation of diabetic cataracts in humans.

Research Needs and Approaches

- Further determination of the chemical pathways involved in diabetic cataract and the mechanism of sorbitol formation by the lens.
- Control of aldose reductase activity by pharmacological inhibitors.
- Characterization of osmotic damage to lens fibers in the diabetic lens.
- Further definition of the transport of glucose and sugars into the normal lens.

Congenital, Metabolic, and Genetic Cataracts

In the United States, the total prevalence of prenatal cataract is 41,000, but not all cases are first diagnosed in childhood. Almost one-third of these individuals are legally blind, many from the permanent sensory deprivation which results from congenital cataract. Unfortunately, the major causes of genetic cataract are unknown.

Accomplishments

Chromosomal defects in patients with congenital cataract have been uncovered. Currently, a number of laboratory animals with inherited congenital cataract are being studied in order to obtain information on the transmission of cataract-producing genes.

Maternal infection by the German measles (rubella) virus during the first trimester of pregnancy can cause congenital cataract in newborn babies. The isolation of rubella virus from human cataract by NIH-supported investigators during the 1964-65 rubella epidemic in the United States provided direct evidence that viruses can cause cataract in humans. It is now known that herpes simplex or chicken pox can also induce human cataracts, and other viruses are suspected of having this capability. A marked reduction in the incidence of rubella cataract during the past five years can be traced to successful mass rubella vaccination programs.

Certain congenital cataracts are associated with inborn errors of metabolism. These include such errors of carbohydrate metabolism as galactosemia and galactokinase deficiency. In such conditions, carbohydrates derived from milk can accumulate in the blood of newborn babies because of a genetically determined enzyme deficiency. The lens accumulates products of galactose metabolism which in turn leads to cataract formation. Galactosemic babies who are raised on a milk-free diet can develop normally and avoid cataract. Studies in which galactosemia is simulated in laboratory animals continue to provide excellent models for the mode of action of toxic carbohydrates on the lens and the prevention of such effects by use of aldose reductase inhibitors.

Other inborn errors of metabolism which can cause cataract include mannosidosis, Fabry's disease, Wilson's disease, hypoglycemia, Lowe's syndrome, and hypoparathyroidism. The latter disorder causes low blood calcium and thereby depletes the lens of the calcium ions it needs for normal metabolism. In certain of these conditions, early recognition of the problem and prompt treatment can result in complete or partial reversal of the cataract.

Research Needs and Approaches

- Definition of chromosomal characteristics in animals and humans with cataract and determination of how genes regulate the differentiation of lens fibers.
- Investigation of the cataractogenic effects of viruses.
- Study of the lens epithelium and fiber culture in test tubes.
- Development of methods for studying systemic metabolic abnormalities in human congenital or developmental cataract.
- Determination of the effect of calcium on lens transport and metabolism.

Cataract Induced by Drugs and Radiation and Occurring Secondary to Other Eye Disorders

Cataract can result from high doses of certain drugs or be caused by other ocular disorders. In the latter case, it may aggravate existing visual impairment.

Cataract can develop in patients who are receiving large doses of systemic corticosteroids and from the prolonged application of corticosteroid eyedrops to the eye to control inflammation.

Experimental studies on animals and extracted human lenses indicate that near-ultraviolet light may have deleterious effects on lens transparency. This has led to speculation that chronic ultraviolet radiation from either the sun or artificial sources could contribute to the development of cataracts in humans. There is no evidence to support this hypothesis at the present time, but the subject deserves further investigation.

Damage to the lens caused by trauma accounts each year for a major part of the impairment of the 198,000 people who suffer open wounds of the eye in the United States. Visual impairment in people suffering from retinitis pigmentosa or related retinal degenerations may be further aggravated by cataracts. Many such patients require cataract surgery to preserve the minimal sight remaining to them.

Accomplishments

Drug-Induced Cataracts. NEI-supported studies of the rabbit lens in tissue culture have shown that steroids affect the lens in part by increasing the permeability of lens cell membranes, thereby allowing abnormal movement of ions to take place. Recent research has also clarified the mechanisms by which echothiophate, chlorpromazine, and triparanol—all used to treat either ocular or systemic conditions—cause cataract.

Ultraviolet Light in Cataract Pathogenesis. The concept that ultraviolet light can induce cataractous changes in the lens is based on studies of rodents and observations of chemical alterations in excised human lenses and in isolated proteins. Again, there is no evidence that ultraviolet light in nature causes cataract, but this is an important concept to pursue.

Cataract and Other Eye Disorders. Recently, promising results have been obtained in treating cataracts caused by injury by adapting surgical instrumentation originally designed for removal of diseased vitreous humor. In cataract resulting from inflammation, one group of investigators has recently succeeded in identifying a plasma lipid as the main cataract-inducing agent in uveitis. Attempts are now being made to prevent the cataract-causing effects of this lipid by blocking its action. It also appears that lysophospholipids may potentiate the toxic effects of corticosteroids on the lens by opening up the spaces between the lens membranes, thereby making the drug accessible to the lens fibers.

Research Needs and Approaches

- Determination of the mechanism of drug-induced cataracts and cataracts which result from lens injuries.

- Investigation of the chemical factors in the aqueous humor that contribute to cataract formation.
- Investigation of the role of radiation, including ultraviolet light, in cataractogenesis.

With regard to the latter, epidemiologic studies are needed which compare various levels of light exposure with cataract incidence among non-migrating populations.

Dislocated Lens

The lens is held in place by zonular fibers. A significant number of adults suffer visual impairment due to inherited disorders or injury of the zonules which lead to dislocation of the lens.

In addition to reduced visual acuity, a dislocated lens causes disturbances of size, shape, and color of the retinal images. In children age six or younger, these visual abnormalities result in irreversible visual loss due to amblyopia. Furthermore, when the lens is dislocated, secondary damage to the eye such as glaucoma can result.

Accomplishments

During the past ten years, NEI-supported investigators have found two major types of the disease homocystinuria, an inborn error of metabolism which causes dislocated lens. One type can be corrected by administration of vitamin B_6 whereas the other cannot.

In two laboratories, studies of the anatomical structure and chemical composition of the lens zonules in humans and laboratory animals are in progress. These studies have clarified some of the possible genetic or chemical abnormalities which cause dislocated lenses in humans. Possible abnormalities in structural protein composition are being sought in patients with inherited Marfan's syndrome also associated with dislocated lenses.

The optical effects of the dislocated lens can often be at least partially corrected by an eyeglass or contact lens. In selected cases, the use of modern surgical techniques has made possible the successful removal of dislocated lenses; however, it is a difficult procedure which poses some risk to vision and to the eye itself.

Research Needs and Approaches

- Determination of the structural protein composition in Marfan's syndrome and study of other genetic disorders causing lens dislocation.
- Investigation of the structure and function of the zonules.
- Development of surgical methods for correction of dislocated lenses.
- Improvement of optical corrections for children with dislocated lenses.

Accommodation and Optical Problems of Cataract and Aphakia

Accommodation. The refractive power of the lens must vary in order to provide clear images of objects at various distances. When focusing at near ranges, the lens changes in shape, a process known as accommodation. The ability to accommodate varies with age, being greatest in the infant and child and decreasing progressively as one gets older. After age 40, the accommodative power of the lens decreases to the point that images cannot be focused on the retina if the object is held at a normal reading distance less than ten inches from the eye. Thus, reading glasses are needed. This partial loss of accommodative power is known as presbyopia, and everyone age 40 or older is affected.

Optical Problems of Patients with Cataract. The swelling of the lens which occurs during early cataract formation induces myopia and thereby a condition in which the size of the retinal images of the two eyes are different. The effect this has varies from individual to individual and depends in great part on the degree to which the two eyes may be affected by developing cataracts. In some people, this condition may cause significant visual problems which require special optical correction.

Optical Problems of Aphakia and After Cataract Surgery. People who have undergone successful cataract extraction have varying degrees of satisfaction. More sensitive individuals are troubled by image size differences which are inherent in the use of eyeglasses to correct aphakia following cataract surgery. They may be bothered further by the weight of the eyeglasses, distortions, and blind areas and restrictions in the visual field.

The problem is particularly great when only one cataract has been removed because there are substantial image size differences between the two eyes. An eyeglass correction results in an approximate 20 to 25 percent difference in image size between the two eyes which is totally unreconcilable. Although contact lens correction results in only a 9 percent image size difference, recent evidence indicates that many individuals cannot fuse images of even this amount of disparity, despite previous opinions to the contrary.

Absence of the lens in infants and children, resulting from either hereditary or congenital factors or following cataract extraction, presents special problems. If the eye is otherwise normal, it is critical to provide a suitable optical correction as soon as possible if permanent visual loss from sensory deprivation is to be prevented.

Accomplishments

Accommodation. The interaction between the lens and ciliary body and changes associated with aging which occur in that relationship are still unclear. Research has been directed toward developing means of assessing the activity of the stimulated ciliary body. Attempts have been made to correlate electrical measurements of changes in ciliary body contraction to parallel measures of lens curvature. These in turn are considered in relation to age.

Optical Problems After Cataract Surgery. The introduction of the soft contact lens has made possible the immediate visual correction of the newborn child who has either undergone surgery for congenital cataract or who has been born without a lens. Yet, poor understanding of infant eye development impedes helping such children achieve full recovery and/or optimal use of residual function.

In adults, image size differences between a normal and aphakic eye can be corrected with an intraocular lens implant. This is one of the true advantages of such a device; however, whether this procedure is used depends upon the patient's health status and consideration of both the potential benefits and risks. At present, the great majority of patients receiving an intraocular lens implant for correction of an absent lens are 70 years of age or older.

Research Needs and Approaches

Accommodation. Surprising gaps still exist in understanding of the processes associated with accommodation. For instance, the nature of the stimulus (or stimuli) which controls accommodation is still unknown. Future studies must take into account the important fact that an individual can learn to accommodate voluntarily without the presence of any stimulus per se. This suggests that a combination of voluntary effort and image quality may be implicated in learning accommodative response.

Another important area of investigation that should be pursued is how accommodation causes stretching of the retina and whether this stretching is increased as more effort is required to accommodate with aging. If so, it is possible that accommodation may in some cases play a role in retinal detachment.

Optical Problems After Cataract Surgery. There is a paucity of data on the optical problems of the infant eye. Research is needed to determine such factors as the normal development of the lens and of the refractive power of the lens or cornea. Otherwise, planning for optical correction of children without lenses is subject to significant error.

Glaucoma

Introduction

Glaucoma has long been recognized as a condition in which the intraocular pressure is generally higher than in normal eyes. In the eye, a fluid called aqueous humor circulates between the cornea and lens, bathing and providing nourishment to these tissues. The aqueous is constantly produced by the ciliary body, and it normally flows from the eye through a tiny drainage system into the bloodstream. If this normal outflow becomes obstructed from any one of a number of causes, a buildup in pressure within the eye occurs. In association with this elevated pressure, the optic nerve tends to become deformed at the site where it emerges from the eye, and some or all of its fibers may die. Vision is lost in proportion to the nerve fiber loss, resulting in complete blindness in the worst cases and a characteristic contraction of the visual field in the others.

Gradually, it has become evident that some 30 to 40 different types of glaucoma are known, each having different underlying causes. Some types are very common, others very rare. It so happens that some of the relatively rare types are the most difficult to treat and most likely to cause severe loss of vision. It is increasingly important to learn more about these various causes as a basis for designing specific means of treatment or prevention for the various types of glaucoma. For this reason, the *Glaucoma* Panel places much research emphasis on the subprogram *Etiology of Glaucoma*, the assignment of cause.

Emphasis is also placed on *Optic Nerve and Vision Changes in Glaucoma* because it is necessary to learn how and why the optic nerve becomes deformed and nerve fibers die in order to improve means of protecting and preserving them. Research on *Hydrodynamics of the Eye* will help make clear how circulation of fluids within the eye derived from the blood influences intraocular pressure, and how fluid exchanges are influenced by hormones, nerves, and drugs.

Finally, emphasis on *Treatment of Glaucoma* complements the preceding areas by applying the knowledge gained therefrom to improving means of curing or preventing this disease.

Although many research needs and opportunities exist in each of these fields of glaucoma research, one important need relevant to all of them is for some practical means of measuring intraocular pressure at home, much as blood pressure can now be easily checked at home. A simple, inexpensive home tonometer could contribute valuable information to studies of low tension glaucoma, of the circadian variations in intraocular pressure, and of responses to medication.

Importance

Glaucoma is a common and serious eye disorder. One or two of every hundred adults have intraocular pressures sufficiently above normal to require periodic reexamination to check for increasing pressure or signs of damage to the optic nerve that may require medical or surgical treatment. Each year, approximately 178,000 new cases of glaucoma are diagnosed. The disease affects the vision of more than 1 million people in the United States, causing visual impairment in over 200,000, of whom 56,000 are legally blind. Women are affected more often than men.

Each year nearly 2 million visits are made to ophthalmologists' offices or hospital eye clinics for diagnosis and care of glaucoma, accounting for 1 of every

16 visits for eye diseases or injuries. Eye surgery for glaucoma costs an estimated $8.8 million per year. However, the great majority of patients who have glaucoma are treated by means of eyedrops and other medications rather than by surgery. In the United States, the total patient cost for one year for one type of eyedrop used in treating glaucoma has been estimated at $29 million. Thus, besides being a widespread and often serious eye disease, glaucoma is an expensive one.

Accomplishments

Medical and surgical treatments for glaucoma have been repeatedly improved as a result of laboratory and clinical research. Advances that have been made in distinguishing different types of glaucoma from one another have led to fundamental clinical advances in selecting the best treatments. The causes of several types of glaucoma have been explained, leading to still better treatment. Excellent instruments for measuring and detecting abnormal intraocular pressure have been devised. Inspired by the research of a small number of pioneer investigators and supported mainly by federal grants for research and training, a large and diverse group of people have dedicated their careers to better understanding of glaucoma and its treatments. Specific accomplishments in this field are described under the appropriate subprogram headings.

Goals of Glaucoma Research

- Improve detection and diagnosis of glaucoma to identify patients needing treatment.
- Discover the causes of the various forms of glaucoma and how they destroy vision.
- Find out how to cure or control the various types of glaucoma and prevent loss of vision.
- Rapidly relate the results of experimental and clinical investigation to the management of clinical problems.

Etiology of Glaucoma

Developmental Glaucoma

Fortunately, the developmental anomalies of the eye that cause glaucoma are rare. Nonetheless, they are a significant problem because they may lead to severe and permanent loss of vision at an early age. Though a majority of patients may benefit dramatically from surgery in infancy, those that do not often require repeated hospitalizations and repeated surgical procedures under general anesthesia.

Several types of developmental glaucoma exist, and early differential diagnosis is important to the choice of treatment. Although it is unrealistic at present to think of eliminating developmental glaucomas entirely, it should be possible through research to reduce their incidence and the degree of visual loss they cause.

Accomplishments

Progress against a type of glaucoma associated with a congenital lack of the iris may be cited as an example of recent accomplishments in this area. Studies supported by the National Eye Institute have shown that in such cases the small fragment of iris that is present at birth can block the drainage of aqueous fluid from the eye, causing the intraocular pressure to rise. Although it is possible to treat this disorder medically and surgically with varying success, recognition of the responsible mechanism has pointed the way to its possible prevention. The effectiveness and safety of surgical separation of the iris fragment from the outflow channel is now being evaluated.

Research Needs and Approaches

Many clinical features of developmental glaucoma remain to be described, and proposed treatment programs require testing. New drugs and drug delivery systems and new forms of surgery need to be evaluated. Genetic and environmental factors should be sought. There is also need and opportunity for developing ways of objectively assessing the status of the infant visual system.

More needs to be learned about the type of glaucoma that occurs following surgery for congenital cataract. Means of detecting any tendency to glaucoma before surgery and improved understanding of how this condition is induced would likely lead to earlier diagnosis of this condition and possible modification in the cataract extraction technique, resulting in a reduced incidence of this type of glaucoma.

Research in this area could be made most economical and effective by developing a small number of clinical centers which could attract sufficient numbers of patients for adequate study. In addition, a national registry for surgical or postmortem specimens could help in a study of the rarer forms of developmental glaucoma.

Primary Open-Angle Glaucoma

Primary open-angle glaucoma is the most common form of the disease and is also the cause of much of the visual loss associated with glaucoma. In this condition, the intraocular pressure may become gradually and progressively elevated without symptoms and may significantly reduce the field of vision in one or both eyes before it is noticed by the affected individual.

Accomplishments

When primary open-angle glaucoma is diagnosed early, at the very onset of damage to the optic nerve, it usually can be adequately controlled during the patient's lifetime by medical and/or surgical treatment. Only in a small number of cases in which diagnosis has been made early does severe loss of vision occur in spite of all therapeutic efforts. In general, the more advanced the disease at the time of diagnosis, the poorer the prospect of retaining vision. Improved means of both early detection and treatment are therefore needed.

In recent years, research on the genetic aspects of primary open-angle glaucoma has been of particular interest because many patients have a definite family history of the disease. Experimental studies have shown a difference in response to corticosteroid drugs between glaucoma patients and those without the disease. However, because of some variance in the findings of different investigators concerning this phenomenon, further work in this area is indicated.

Research Needs and Approaches

Although great improvements have been made in controlling open-angle glaucoma and preventing blindness, it is not possible to cure the disease. Treatment generally consists of reducing intraocular pressure by suppressing the formation of aqueous humor or facilitating its outflow from the eye. Perhaps if the most fundamental details of the cause of obstruction to fluid outflow were understood, more specific and effective modes of treatment, and even means of cure and prevention, could be developed. However, research on primary open-angle glaucoma is handicapped because this disease occurs exclusively in human beings and therefore must be investigated principally in human eyes.

More research into the genetic basis for primary open-angle glaucoma is needed including studies to demonstrate at biochemical and cellular levels the differences between people with and without glaucoma.

There is statistical and clinical evidence that Black men in the United States may be prone to develop open-angle glaucoma at an earlier age and with more serious damage to the optic nerve and vision than generally occurs in the White population. This finding should be subjected to research which compares populations of Black and White people of similar age and geographic distribution in order to determine what the basis for this greater susceptibility may be.

Primary Angle-Closure Glaucoma

Primary angle-closure glaucoma is a very important form of the disease, ranking only after open-angle glaucoma in prevalence but differing in cause, diagnosis, and treatment. It can develop and cause blindness with extraordinary rapidity, and if the disease is not detected and treated soon enough, some patients become blind in both eyes.

Angle-closure glaucoma is caused by contact of the iris with the aqueous humor outflow channel in the angle between the iris and cornea. It is generally caused by an abnormally shallow anterior chamber—the space between the cornea and the lens—and an abnormally narrow angle where the iris meets the cornea. It is through the angle that aqueous fluid drains from the eye. Treatment of angle-closure glaucoma is primarily surgical and, if done in time, is highly successful in curing the condition and saving sight.

Accomplishments

Impressive progress has been made in recognizing the causes of angle-closure glaucoma and in diagnosing and treating it, but more eyes would be saved if diagnosis could be made earlier, thus permitting not only early treatment but prevention.

Research Needs and Approaches

One problem in angle-closure glaucoma is that simply measuring the pressure in the eye does not provide a warning of impending attack. In addition, many eyes that appear to have the anatomical peculiarities associated with angle-closure glaucoma never develop the disease. Moreover, eyes with normal anatomy can develop the condition if something pushes the lens forward against the back of the iris. Therefore, there is need to improve diagnostic and predictive procedures in order to define within narrower limits those patients at high risk.

Studies of the variable effect of miotic eyedrops—those which constrict the pupils—on people predisposed to angle-closure glaucoma need to be pursued. In some of these patients, the drugs cause the angle to become wider; in others, they cause the angle to close and thereby precipitate glaucoma.

Although surgery for angle-closure glaucoma may succeed in completely reversing the condition and restoring the outflow system to normal, in other cases the iris adheres in some places to the outflow channels and obstructs the outflow of aqueous humor. Additional research is needed to determine why this iris adhesion occurs and whether it would be feasible to attempt to separate it. In addition, further research is needed to determine whether the aqueous outflow system can be damaged by repeated attacks of angle-closure glaucoma, even without the formation of iris adhesions.

A rare complication of surgery for angle-closure glaucoma in which the pressure becomes high but does not respond to the usual medications and operations has traditionally been referred to as "malignant glaucoma" because it so rarely responded to treatment and so commonly led to blindness. Although thanks to new drug and surgical treatments it can now be relieved in nearly all cases, malignant glaucoma deserves more systematic study, for it seems to involve fundamental mechanisms that may underlie other forms of angle-closure glaucoma and the effect of miotic eyedrops. In fact, malignant glaucoma may represent an extreme combination of circumstances that may occur in ordinary cases of angle-closure glaucoma.

Secondary Glaucomas

In the various kinds of secondary glaucoma, intraocular pressure becomes elevated as a result of some recognizable preexisting condition such as inflammation, degenerative changes, trauma, or neoplasm. The secondary glaucomas are not the most common type but are among the most difficult to treat and cause a disproportionately high incidence of blindness. This is particularly true of the kind caused by uveitis.

For each type of secondary glaucoma, better understanding of the underlying disease process and the mechanism by which it raises the intraocular pressure is needed. This, it is hoped, will lead to development of specific forms of treatment for each condition. Because it seems likely that this approach will require a long time and a great deal of effort, and because in the meantime a great many people are losing their vision and in some cases suffering pain from secondary glaucoma, there is immediate need for less ideal but palliative treatments that reduce intraocular pressure without curing the underlying disease.

At present, secondary glaucoma is treated with nonspecific, general methods of reducing pressure, such as oral carbonic anhydrase inhibitors and epinephrine eyedrops. For glaucoma secondary to inflammation, nonspecific anti-inflammatory drugs are used. In other cases, miotic eyedrops may be

administered and, when medical means fail, surgery is employed to improve drainage of aqueous humor from the eye. Although of great value, these treatments are often inadequate for maintaining sufficient reduction of pressure to preserve vision.

Accomplishments

Improvements in anti-inflammatory agents have reduced the frequency of glaucoma due to inflammation. Advances have been made in studies of the role of prostaglandins in causing inflammation and secondary glaucoma. Other accomplishments concerning the specific types of secondary glaucoma are covered in the following discussion of Research Needs and Approaches.

Research Needs and Approaches

Uveitis and Secondary Glaucoma. Research has concentrated primarily on animal experiments in which prostaglandins and related substances have been used to produce inflammatory reactions resembling acute uveitis that cause an acute rise in intraocular pressure. These experiments have raised speculation that prostaglandins and related compounds may have a role in human uveitis and associated secondary glaucoma. Further research is needed to determine whether this class of compounds does in fact have an etiologic role in this condition and whether inhibitors of prostaglandins can be successfully applied to the treatment of uveitis and secondary glaucoma.

More study is needed to explain why pressure is elevated in some cases of uveitis and not in others and what actually occurs in the aqueous outflow channels and in the ciliary body to cause this condition. Clinicopathologic studies of aqueous humor in tissue samples removed during surgery are promising approaches. In addition, there should be more study of uveitis experimentally induced in primates.

Exfoliation Syndrome and Glaucoma. A significant number of people who appear to have otherwise ordinary primary open-angle glaucoma have the exfoliation syndrome, in which a fine, gray material is seen on the front surface of the lens, the back of the iris, and elsewhere in the eye. Also, pigment from the iris is often found scattered in the angle. Exfoliation glaucoma commonly affects a patient's eyes unequally, and it tends to be less responsive to standard medical treatment than primary open-angle glaucoma.

There is evidence that exfoliation glaucoma is not related to primary open-angle glaucoma, and if this can be definitely proved, it could open up a potentially large and important area for research on the cause of this condition. The ultimate aim of such studies would be to develop methods for stopping the formation of exfoliation material and preventing or alleviating the glaucoma.

More effort should be expended to study this condition including chemical analyses of exfoliation material and tissue culture preparations of lens epithelium and other cells associated with exfoliation material in human eyes which are obtainable at autopsy.

Hemolytic Glaucoma. In this form of secondary glaucoma, hemorrhage into the vitreous humor or into the anterior chamber produces severe open-angle glaucoma. This condition most commonly results from injuries to the eye but also may develop as a complication of vitrectomy, the operation used to remove severe hemorrhages associated with diabetic retinopathy.

Hemolytic glaucoma responds poorly to standard medical and surgical treatment, especially if there is a considerable amount of hemorrhage in the vitreous humor. Better forms of treatment are needed.

Research on the cause of hemolytic glaucoma has shown that when red blood cells from the hemorrhage age, they turn into "ghost" cells that can severely obstruct the normal drainage of aqueous humor from the eye. The resulting retention of fluid causes glaucoma. There is need to discover whether it may be possible to fragment or change the physical character of the ghost cells to relieve the obstruction.

Lens-Induced Glaucoma. Secondary glaucoma resulting from degenerating lens material obstructing outflow channels is a relatively uncommon but important form of glaucoma that may lead to loss of vision and even necessitate removal of the eye if not recognized early and properly treated. One of the main problems is to distinguish the various forms of lens-induced glaucoma and to separate them from glaucomas resulting from other causes such as uveitis or tumors. If the lens is found to be responsible, its surgical removal can cure the glaucoma.

Research supported by the National Eye Institute has shown that lens proteins, without cells, can obstruct aqueous outflow in enucleated human eyes, but whether this occurs in life remains to be determined. Noninvasive methods for detecting lens proteins in the anterior chamber should be devised for both research and diagnostic purposes. Development of nonhuman primate models of lens-induced glaucoma would be helpful to investigations of the origin of this condition and to the development of possible new treatments.

Neovascular Glaucoma. This frequently painful form of glaucoma causes many cases of visual loss and occurs as a complication of many diseases in which retinal ischemia is a factor. Neovascular glaucoma occurs when abnormal blood vessels proliferate on the iris and in the angle, obstructing the outflow channels. Once the condition is fully developed, its treatment has been most unsatisfactory. Research is clearly needed on the pathogenesis and treatment of this condition to determine conclusively whether photocoagulation of the retina or direct laser coagulation of new vessels in the angle can prevent the development of neovascular glaucoma, as it now appears able to do. Research is also needed to identify possible factors that may stimulate new blood vessel formation in the iris and angle.

For these purposes, there should be a greater effort to develop animal models of neovascular glaucoma.

Pigment Dispersion and Glaucoma. A frequent and puzzling clinical finding is the dispersion of pigment from the back of the iris to the back of the cornea, the front of the iris, and the angle of the anterior chamber. This condition is found mostly in myopic young adults. In some cases, it occurs without elevation of pressure or evidence of glaucoma, but in others, it is accompanied by open-angle glaucoma.

This entity has been called "pigmentary glaucoma," but what its relationship may be to primary open-angle glaucoma, to congenital defects of the angle, or to abnormalities in the retina and choroid is still disputed. This form of glaucoma can be mild, with exacerbations and remissions, or it can be severe enough to require surgery.

Clinical investigations are needed to determine how often people with pigment dispersion, but without glaucoma, are in danger of developing glaucoma and to determine the fate of young adults with this condition when they become older. It is important to determine to what extent environmental and genetic factors and treatment influence the course of this condition. Tissues of the aqueous outflow system and portions of the iris removed during filtration surgery should be examined, and further study in tissue culture would be advantageous. Even better would be the development of an animal model of pigmentary glaucoma.

Retinal Detachment and Secondary Glaucoma. A reversible type of open-angle glaucoma occurs on rare occasions in association with retinal detachment but is relieved when the retinal detachment is repaired. Why this occurs is a mystery which, if solved, could reveal something fundamental about both glaucoma and retinal detachment.

Epithelial Invasion and Glaucoma. Invasion of epithelial cells from the outer surface of the eye in the form of a spreading sheet or cystic growth is a serious complication of eye surgery and sometimes of accidental injury to the eye. It may end with glaucoma and loss of the eye. Although not common, it is a serious problem, and surgery has only occasionally proved successful. Very little basic research has been done on this problem, and it is not known why epithelial invasion almost always takes place in eyes without a lens or in those in which the lens has been injured.

Further research is needed to gain knowledge of the factors that influence intraocular epithelial growth and the mechanisms underlying the associated secondary glaucoma. An animal model should prove especially helpful for investigating growth-promoting factors and their inhibition and for testing possible means of treatment. Tissue culture of surgical specimens from cases of epithelial invasion is another approach to be considered.

A promising approach in this and several other of the secondary glaucomas which deserves additional attention is the examination of aqueous humor samples from patients. Improved examination methods have made it possible to identify and study cells and particles associated with secondary glaucoma and to correlate these findings with what is seen in tissues of the aqueous outflow system that are excised when surgery for glaucoma must be performed.

Optic Nerve and Vision Changes in Glaucoma

The optic nerve can be damaged and vision destroyed by every type of glaucoma. In most instances, this is attributable to the effects of abnormally elevated intraocular pressure. But as yet, there is very little understanding of the manner in which pressure damages the optic nerve. And, susceptibility to such damage varies considerably with the individual. In some people, the optic nerve apparently remains normal for years despite pressures far above normal; in others, the optic nerve becomes severely damaged, and vision is lost, with only slightly elevated pressure. There is even one rare type of glaucoma in which optic nerve changes and visual loss occur with no evident elevation of pressure, a condition known as "low tension" glaucoma.

Optic nerve and vision changes in glaucoma constitute a very important category in glaucoma research, for they are the ultimate problem in this disease. The goal of all efforts to detect glaucoma and reduce intraocular pressure is to prevent optic nerve damage and consequent loss of vision.

Accomplishments

In recent years research has increased considerably on the cause of the characteristic abnormal cupping or depression and atrophy in the optic disc—the area where the optic nerve joins the retina—associated with glaucoma. Attention has focused particularly on evaluating the possible effects of intraocular pressure on the blood supply to the optic nerve.

The principal clinical criteria for determining glaucomatous changes in the optic nerve head have been observations of changes in cupping and the development of visual field defects. Until recently, observation of these changes has depended solely upon the experience and skill of the observer. Now, stereophotography, used in conjunction with visual field measurements, has been introduced to improve the sensitivity and objectivity of appraising optic disc damage as a measure of a patient's progress and as a guide to therapy.

Research Needs and Approaches

Relationship Between Optic Nerve Head Cupping, Intraocular Pressure, and Field Loss. These relationships are very important to consider and investigate. Characteristically, in chronic glaucoma with moderately elevated intraocular pressure, abnormal cupping of the optic nerve head develops slowly, and defects in the visual field gradually become evident. However, in acute angle-closure glaucoma, in which the intraocular pressure rapidly becomes very high, the optic disc can be damaged severely without preliminary cupping. This varying effect points up the problem in investigating chronic glaucoma in laboratory animals with an acute, high-pressure, short-duration type of glaucoma. A primate model of chronic, mildly elevated pressure is needed which will permit study of effects on the optic nerve head over a long period.

Another very important question is the varying relationship between moderately elevated pressure and the rate and severity of damage to the optic nerve head among different people. Why there should be such a broad range of vulnerability is unexplained.

Reversibility of Cupping and Field Loss. Occasionally, when elevated intraocular pressure is reduced to normal or below normal levels, optic nerve cupping can dramatically disappear and the visual field can appreciably improve. This occurs most frequently in children, but occasionally it is seen in adults. These findings suggest that elevated pressure may directly influence the form of the optic disc or the water content of disc tissues in some manner that is rapidly reversible when the pressure is reduced. It also suggests that part of the loss of visual field caused by elevated pressure may in some cases be at least partially reversible.

Research should be directed toward clarifying the way in which the optic disc may be deformed and its function impaired, either reversibly or irreversibly, in relation to elevation and reduction of intraocular pressure. This requires both clinical study and the creation of a subhuman primate model in which optic nerve changes in response to controlled variations in pressure can be studied.

Blood Supply. A considerable amount of research in recent years suggests that the blood supply to the optic nerve head is somehow critically involved in glaucomatous damage. Such studies have provided information about blood circulation in the optic nerve head, but they have not yet provided a description of what occurs in glaucoma nor much that is of predictive or therapeutic value. New and ingenious approaches are needed for study of this relationship.

Role of Systemic Blood Pressure. There is need for a planned, systematic appraisal of the relationship of systemic blood pressure to the vulnerability of the optic disc in glaucoma. Further, there is a need to assess whether reducing high blood pressure increases the susceptibility of the optic nerve to damage by elevated intraocular pressure. This information would be vital for internists who must decide how much they should seek to reduce the blood pressure of patients who have not only systemic hypertension but increased intraocular pressure.

Predictive Factors. Some means of determining in each individual case the susceptibility of the optic nerve head to damage by a given degree of elevation of intraocular pressure is greatly needed. Preliminary studies to develop such tests are promising and need to be pursued further. If established, a reasonably reliable predictive measure of vulnerability of the optic nerve would provide an extremely valuable aid to the ophthalmologist in deciding when and how intensively to start treatment of an individual with elevated intraocular pressure.

Improved Visual Field Testing. Present difficulties in achieving systematic and reliable visual field testing in everyday practice make improved automatic testing methods desirable. Although this may be difficult, it is an important area for research because lack of good visual field information hampers many clinical decisions.

Low Tension Glaucoma. This condition is said to occur in patients whose optic nerve is extraordinarily susceptible to cupping and atrophy when the intraocular pressure is only at the upper end of what is usually considered the normal range. Though the disease is not very common, research on low tension glaucoma is of great importance not only for the sake of people losing vision from it but for what it can add to understanding of the mechanism of optic nerve damage that occurs in ordinary glaucoma. Home tonometry should be used as extensively as possible in studying people who may have low tension glaucoma.

Hydrodynamics of the Eye

Except for low tension glaucoma, elevation of intraocular pressure is the common characteristic of all forms of glaucoma. The flow of fluid into, through, and out of the eye must be studied to learn what factors underlie the normal regulation of intraocular pressure and the failure of this process in glaucoma.

Accomplishments

Research on ocular hydrodynamics in relationship to glaucoma has involved many of the leaders in ophthalmology during the last hundred years. Their work has shown that the main determinants of pressure within the eye are the rate of aqueous humor formation, resistance to aqueous outflow, and recipient venous pressure. Furthermore, it is now understood that most forms of glaucoma are due to obstruction of aqueous outflow.

Much has been discovered concerning the way in which aqueous humor is secreted and diffused, properties of aqueous outflow in primates, the effects of drugs, and the influences of the nervous system and blood circulation. Some light has been shed on the causes of outflow obstruction; yet, despite the work of a hundred years or more, it is remarkable how many key pieces of information are still missing which are essential to full understanding and complete control or prevention of glaucoma.

Research Needs and Approaches

Formation of Aqueous Humor. The rate of formation of aqueous humor and aqueous outflow are the prime determinants of the level of intraocular pressure. For better understanding and improved treatment of all types of glaucoma, it is essential that more be learned about the mechanisms of aqueous formation and the factors that may control it.

The role of prostaglandins in aqueous formation has been of particular recent interest. This group of compounds has been found to raise the intraocular pressure in rabbit eyes by causing increased fluid inflow, blood vessel dilation, and breakdown of the barrier between the blood and aqueous humor. This has led to speculation about possible involvement of prostaglandins in human glaucoma that develops secondary to injury or inflammation. Much more research on this question is required, including evaluation of whether drugs that interfere with prostaglandins may be useful in treating uveitis and secondary glaucoma.

Generally, it is more desirable to study aqueous humor formation in primates rather than in subprimates if the aim is to apply new information eventually to clinical problems. For human studies, direct but noninvasive methods for measuring and monitoring aqueous humor formation are needed.

Because it is likely that intraocular pressure affects aqueous formation in part by influencing the rate of blood flow through the ciliary body, additional research in this area is needed as well. There is also an urgent need to clarify the metabolic processes involved in aqueous humor formation.

The mystery of why carbonic anhydrase inhibitors which are administered orally to reduce aqueous formation in glaucoma patients have no effect when applied topically to the eye requires investigation and clarification. In fact, research to obtain a complete understanding of the action of carbonic anhydrase inhibitors on aqueous formation should have high priority, for it promises to provide important insight into the physiology of aqueous formation and may lead to development of improved means for medical reduction of intraocular pressure.

There is also need to search for substances which may increase the rate of aqueous formation because these could be useful in treating excessively low intraocular pressure (hypotony) and might be helpful in elucidating the mechanism of low tension glaucoma.

Outflow of Aqueous Humor. Among the many opportunities for productive research in this area, metabolic studies of the tissues that lie between the anterior chamber and Schlemm's canal—the outflow channel through which aqueous fluid drains from the eye into the venous system—are long overdue. Clarification of how these tissues respond to drugs and hormones is important to the understanding of the role of metabolism in modulating aqueous outflow. The mechanism underling glaucoma induced by corticosteroids and the manner in which various drugs and chemical substances influence aqueous outflow in normal and glaucomatous eyes should be studied.

Uveo-Scleral Functional Relationships. So-called uveo-scleral outflow, in which a fraction of the aqueous humor passes through the ciliary muscle to the choroid and sclera, has been shown to be independent of intraocular pressure but dependent on the compactness of the ciliary muscle. This phenomenon has been studied in animals, but little is known about whether it occurs in humans. The rate of aqueous humor formation in humans is known, however, to be reduced by detachment of the choroid and ciliary body, a complication of glaucoma surgery and occasionally of surgery for cataract. Although improved means of preventing or treating this condition are needed, elucidation of this phenomenon could also provide new and better approaches to controlling elevated intraocular pressure in glaucoma, and the possible relationship of this occurrence to uveo-scleral flow should be further investigated.

Circadian Variation of Intraocular Pressure. Spontaneous, periodic variation in intraocular pressure in open-angle glaucoma remains one of the most important and least understood enigmas in this field. Whether variation in intraocular pressure is attributable to variations in aqueous humor formation or to change in resistance to aqueous outflow needs to be established. This phenomenon is of

great importance in glaucoma research not only for understanding basic mechanisms but because of the possibility it suggests for exploiting a natural mechanism for achieving better control of intraocular pressure.

A noninvasive clinical device for constantly monitoring intraocular pressure would be particularly valuable when used in conjunction with methods for measuring the rate of aqueous flow. Such devices have already been developed for use in animal eyes, but a device that would be comfortable and provide precise measurement in human glaucoma patients has not yet been achieved.

Vitreous Humor Barrier Properties. More research is required on the characteristics of fluid movement through the vitreous humor and across the vitreous face, particularly in relation to the influence this may have on the depth of the anterior chamber of the eye. There should be more research to define how vitreous volume, in turn, responds to changes in the anterior chamber caused by miotic drugs.

Medical and Surgical Treatment of Glaucoma

Glaucoma treatment continues to rely principally on drugs: miotics, epinephrine, and carbonic anhydrase inhibitors for the primary glaucomas, and corticosteroids for glaucoma secondary to uveitis.

For certain types of glaucoma, surgical treatment is widely preferred over medical treatment, but these account for only a small fraction of cases. In particular, adults who have primary angle-closure glaucoma and infants who have congenital glaucoma are most commonly treated by surgery. Operations for these conditions are in most cases curative and without great risk; however, in most other types of glaucoma, the usual practice is to reserve surgery for situations in which medical treatment has been tried but has proved inadequate or intolerable to the patient because of side effects.

Accomplishments

Research on medical and surgical treatment of glaucoma has brought valuable advances. The discovery, testing, and clinical introduction of the various glaucoma drugs now in common use have undoubtedly saved the vision of a great number of glaucoma patients, while sparing them from surgery. Even for patients with acute angle-closure glaucoma, drugs have been used to prepare them better for surgery.

Medical treatment for malignant glaucoma, for which there was previously no known effective therapy, is, as a result of research, now successful in half the cases. It is possible that the remaining cases can all be relieved and possibly cured by new surgical techniques applied to the vitreous humor.

Effective use of anti-inflammatory steroid drugs in the eye has significantly improved the treatment of various forms of uveitis and associated secondary glaucoma. The corticosteroids have also been found valuable in reducing tissue reactions to antiglaucoma surgery, thereby raising the success rate of this procedure.

Nonetheless, despite these and other accomplishments in improving treatment of glaucoma, serious needs exist for further fundamental advances in this area.

Research Needs and Approaches

Treatment of Open-Angle Glaucoma. Although the majority of patients with primary open-angle glaucoma respond well to standard pilocarpine and epinephrine eyedrops, these medications must be administered several times a day and may cause intermittent dimming and blurring of eyesight. In addition, these drugs can cause other undesirable side effects and may lose their effectiveness with time.

New drug delivery systems, principally for pilocarpine, provide means for exposing the eye to a constant flow and concentration of medication and reduce the need for frequent installation of drops.

Miotic eyedrops which are stronger than pilocarpine may cause the gradual induction of cataract. However, in facing open-angle glaucoma so severe that it cannot adequately be controlled by conventional therapy, some ophthalmologists and their patients prefer to use stronger miotic eyedrops and take the risk of cataract rather than turn to antiglaucoma surgery. This is because cataracts can be removed with a higher degree of success and lower risk than is encountered in antiglaucoma surgery.

Because of these problems, the search continues for new antiglaucoma medications. Drugs are sought that may either be more effective, more tolerable, carry less risk of cataract, or possess a combination of all these virtues.

Among the new drugs being investigated that seem to offer some of these advantages are the beta-adrenergic blocking agents, which can be used as eyedrops. Extensive clinical testing of these agents is still required.

For many years, it has been supposed that the central nervous system may exert some influence on intraocular pressure. Recent reports of changes in intraocular pressure after the optic nerve is cut and after stimulation of portions of the central nervous system have strengthened this concept. These observations, along with reports of reduction of intraocular pressure by barbiturates, general anesthetics, and marihuana derivatives, indicate a need for further clinical evaluation of the use of psychotropic and other centrally-acting drugs in the treatment of open-angle glaucoma.

New techniques for improving filtration surgery for glaucoma, in which a new outflow channel is made for drainage of aqueous humor from the eye, show great promise but require further clinical evaluation. In general, these new methods provide means for better control of fluid outflow, thereby avoiding excessively low pressure and subsequent detachment of the choroid and flattening of the anterior chamber.

Treatment of open-angle glaucoma by laser puncture of the outflow channels has received much publicity in recent years, and claims have been made of at least short-lived effectiveness. A thoroughly documented, controlled clinical evaluation would be welcome.

Treatment of Angle-Closure Glaucoma. In most cases, medical treatment of primary angle-closure glaucoma is aimed at reducing the intraocular pressure in preparation for surgery. Iridectomy, in which a piece of the iris is removed, is then performed in order to allow the aqueous humor to flow from the posterior to the anterior chamber of the eye. Relieving the excess pressure behind the iris in this manner permits it to settle back away from the outflow channels and lets the aqueous humor regain its normal outflow. This cures the glaucoma. However, if the iris fails to settle back because it adheres to the outflow channels, or if some other mechanism continues to hold the iris in this position, glaucoma will persist. In such cases, other forms of treatment are required.

The drugs most commonly used in medical treatment of an eye with angle-closure glaucoma prior to surgery to help in opening the anterior chamber angle may actually cause an adverse shallowing of the chamber. Using drugs at lower than customary concentrations and doses in the initial treatment of angle-closure glaucoma is a possibility that needs to be tested in a controlled clinical trial.

Laser treatment of angle-closure glaucoma presents both advantages and difficulties but, in selected cases, appears to have succeeded. More investigation and experience is needed before the proper place of laser treatment in angle-closure glaucoma becomes clearly defined.

Treatment of Glaucoma Secondary to Uveitis. Principal reliance continues to be placed on corticosteroid drugs in the treatment of glaucoma secondary to uveitis because noncorticosteroid anti-inflammatory agents have proved considerably less effective. Yet, corticosteroids have potential adverse effects on intraocular pressure and may cause cataracts and unwanted systemic effects. Therefore, safer and effective agents for treating this condition are needed.

Treatment of Neovascular Glaucoma. In addition to the welcome finding that laser photocoagulation of the retina can reduce the risk of blindness from diabetic retinopathy, there is also initial evidence that this treatment can reduce the incidence of neovascular glaucoma, a frequent complication of this retinal disease. There are further indications that it is possible to arrest the development of neovascular glaucoma at an early stage when new blood vessels first develop in the anterior chamber. Laser treatment of the vessels, performed before the intraocular pressure has gone up, appears to be highly promising and to be attended by very low risk. This is a significant development, since neovascular glaucoma as a rule has led to blindness and in many cases produces pain severe enough to necessitate removal of the eye. Therefore, wider evaluation of this new form of treatment is clearly indicated.

Surgical Treatment Problems. Research on glaucoma surgery should be directed toward overcoming common complications and problems. In particular, there is need for further basic research on factors involved in wound healing. In certain individuals, especially young people and children, there is a tendency for the new surgically-created outflow channels to seal over, thereby failing to drain aqueous humor and relieve the glaucoma. This is the crucial reason for treatment failure and blindness in some of the most desperate cases of childhood glaucoma. There is real need to explain and solve this problem. Besides experiments with subhuman primates, study of the healing characteristics of other types of surgical wounds in humans, such as those associated with strabismus and cataract operations, could prove valuable.

When deciding whether to perform filtration surgery for glaucoma in older people, the likelihood of speeding the development of cataract must be taken into account. There has been practically no research to find out why glaucoma surgery may increase the risk of cataract. Certain explanations of this phenomenon have been suggested and need to be followed through in a well-designed, long-term clinical study.

Treatments for the Optic Nerve. As indicated earlier, most treatment for glaucoma, either medical or surgical, is intended to reduce the intraocular pressure. However, other treatment approaches have been proposed and tried from time to time with the aim of directly benefiting the optic nerve, irrespective of pressure. Again, clinical studies are required to test drugs and other substances which might be shown in animal experiments to protect the optic nerve from the effects of oxygen deficiency.

Sensory and Motor Disorders of Vision

Introduction

Normal vision depends upon the coordinated activity of the entire visual system, from neural and muscular mechanisms which control the direction of gaze at objects of interest to the highest levels of brain function involved in visual perception and communication. In its 1975 report, *Vision Research Program Planning*, the National Advisory Eye Council presented an overview of the entire field of visual sensory and motor disorders. In the present report, the Panel has chosen to reaffirm the basic concepts discussed in that first report and to focus on a number of selected topics which it believes are of particular significance at this time. Although presented for the sake of consistency under a subprogram classification, the following five topics constitute the main focus of the current discussion:

1. Disorders Associated with the Development of the Visual System
2. Strabismus and Amblyopia
3. Disorders Affecting the Control of Eye Movements
4. Potential Applications of Neuropharmacology to Disorders of the Visual System
5. The Application of Visual Psychophysical Techniques to the Clinical Diagnosis of Visual Disorders

By selecting these subjects for special consideration, the Council does not intend to imply that the other areas within this field are less important or less deserving of substantial support than they were previously. However, the above areas were selected for two reasons: First, they are not only of great clinical significance, but also amenable to experimental analysis. Second, they are currently among the most intensively and critically studied areas in the field, and as a result of the work of the past decade or so, hold considerable promise for important new developments and breakthroughs.

Importance

Disorders or injuries affecting any part of the complex and highly integrated visual sensorimotor system can lead to serious lifelong difficulties. These include amblyopia, strabismus, nystagmus, abnormalities of gaze, and perceptual dysfunctions. In addition, there are several other conditions caused by vascular, infectious, toxic, or metabolic factors which affect the optic nerve, the ocular muscles, and the visual centers of the brain.

Many of these disorders are of either congenital or developmental origin and therefore are influenced by genetic and early environmental factors. Although in some instances their course may be modified or reversed by visual training or surgery, usually their specific cause is unknown, and at present we have no means of preventing or effectively treating them.

Strabismus, or deviation of the eyes, affects nearly 1.6 million of the 24 million American schoolchildren between the ages of 6 and 11. This is nearly one child in 14. Each year, strabismus necessitates approximately 1.2 million visits to physicians, and an estimated 75,000 hospitalizations are required annually for surgery to correct this condition at a cost exceeding $23 million. A large number

of additional cases come to the attention of optometrists and other eye care specialists who employ orthoptics and optical devices in the treatment of this condition.

Although parents are likely to bring a child with either cross-eye or walleye to a doctor because of their concern about the child's appearance, they usually are unaware of the potential danger of the child's losing vision in the deviated eye, a condition called amblyopia. This condition, which can usually be prevented from causing visual damage if it is diagnosed sufficiently early, necessitates nearly one-half million annual visits to physicians.

Accomplishments

As recently as 15 years ago, almost all research on the visual sensorimotor system depended on the subjective responses of human subjects to visual stimuli. Since that time, electrical recordings from single cells in the visual pathways and brain, advanced techniques of brainwave recording and analysis, and experiments with primates have rapidly led to important new discoveries and renewed insights into how visual information is processed as well as to clues to the possible cause of some sensorimotor disorders.

This information has enabled researchers to take advantage of new techniques which promise to accelerate our understanding of the development and function of the visual system as well as the cellular and molecular basis for its abnormalities.

Aside from the relevance of research in *Sensory and Motor Disorders of Vision* to the improved prevention and treatment of the many diseases included in this category, work in this field has made outstanding contributions to knowledge of the function and disorders of the central nervous system. For example, the demonstration that visual deprivation at a critical stage in the development of laboratory animals can have a profound effect on the subsequent organization and function of the visual system, combined with the development of new methods to investigate such effects, has brought research in this field to the forefront of neurobiological investigation. In fact, many of the most renowned and influential neurobiologists now use the visual system as a model for their studies of the structure and function of neural systems.

Goals of Sensory and Motor Disorders of Vision Research

- Elucidate the normal development, structural organization, and function of the visual system as a basis for better understanding the etiology and pathogenesis of sensory and motor disorders.
- Develop improved diagnostic procedures.
- Develop methods to prevent and control sensory and motor disorders of vision.

Congenital, Developmental, and Degenerative Disorders

The Panel considers the need for basic research on the development of the central visual system as the highest priority in this field. However, important work remains to be done on the normal development of the human eye, on

defects which may occur during its development, and on genetic and acquired abnormalities which may distort the normal pattern of development and lead to impaired vision.

Disorders Associated with the Development of the Visual System

Any useful understanding of the cause, prevention, and/or correction of congenital visual system defects depends upon a much more rigorous understanding of the development of the system than is currently available. Despite considerable progress in describing visual system development, little or nothing is known about the mechanisms underlying it or of the probable causes of the more common developmental abnormalities.

Accomplishments

Normal Visual Development. Studies in lower vertebrates have provided information on several key features in visual development. Although some of the conclusions drawn from these studies are probably generalizable to the visual systems of mammals, including man, many may not be. To some extent this experimental gap has been bridged by the study of chick embryos which in many aspects of their development closely resemble mammals and have the added advantage of being readily available for experimental study.

Developmental Abnormalities. This subject has become a matter of considerable interest in recent years following the first dramatic demonstration of the effects of visual deprivation on the growth of cells in the lateral geniculate nucleus, a key visual processing area of the brain.

Research Needs and Approaches

Normal Visual Development. This is one of the expanding areas of vision research. Several technical developments in the last two years now make possible direct studies of the development of the mammalian visual system in general and the primate visual system in particular. Potentially, such investigations can provide important insights into how the visual system normally develops as well as into human visual abnormalities. Some of these new developments are:

- Thymidine autoradiography, a technique which can be used to determine the time of origin of neurons in the retina and in such central visual structures as the lateral geniculate nucleus and striate cortex.
- Improved techniques for studying mammalian fetuses in the uterus.
- Improved techniques for tracing neural pathways.

To a large extent these new methods, most of which have been developed within the past five years, have replaced more traditional experimental techniques.

One example of their use is the demonstration of alternating bands or stripes within the visual cortex which are related to one or the other eye and of the dramatic effects of early visual deprivation upon the organization of these columns.

- Recent developments in the biochemistry and molecular biology of cell surfaces which have led to the development of procedures for determining cell-to-cell interactions among neurons from different parts of the developing visual system. These approaches offer considerable promise for helping determine how the axons of one group of neurons "find their way" to their appropriate projection sites and make contact with the appropriate class of cells.

Strabismus and Other Oculomotor Disorders

Considerable progress has been made in understanding how normal eye position is maintained, how the two eyes move together, and how this movement is initiated and carried out. In addition, important new developments have occurred in research on the anatomical and physiological consequences of strabismus. Consequently, these subjects have been chosen for special consideration. Much remains to be learned in both these areas concerning the cause of strabismus or disturbed eye movements which occur in many neurological disorders.

Strabismus and Amblyopia

Strabismus affects approximately 5 percent of the population. If uncorrected, it may cause loss of vision, double vision, and loss of the ability to use the two eyes together. Consequently, stereo depth perception may be impaired or absent. Moreover, because of the cosmetic aspects of strabismus, people with this condition often develop emotional problems. Another serious consequence of uncorrected strabismus is amblyopia, reduced visual acuity without apparent defect or disease of the eye, which occurs in approximately 2 percent of the population.

Accomplishments

Past studies of strabismus and amblyopia have added much to knowledge of these disorders but have not revealed their basic cause. Progress has been impeded by the lack of suitable animal models for research. However, recent technological developments have made it possible to produce strabismus and amblyopia experimentally in cats and monkeys. With the availability of the new animal models, a promising beginning has been made toward identifying the effects of abnormal visual experience early in life upon normal visual development.

It has been shown, for instance, that strabismus and amblyopia can cause marked structural and functional changes in visual areas of the brain. These disturbances can be correlated with behavioral changes.

It has also been demonstrated that these conditions occur only during a certain period when the visual system is susceptible to abnormal visual experience. In cats and monkeys, this period ranges from birth to approximately the first three or four months of life. Experimental closure of one eyelid for as little as a few days may be sufficient to cause permanent functional and structural damage to the visual system of these animals.

Research Needs and Approaches

The above findings have demonstrated the importance of removing congenital cataracts or other obstacles to normal vision early in life. They also highlight the importance of determining the best time for performing eye surgery on children to assure both maximum safety and restoration of vision before permanent neural damage results. Further studies may even eventually lead to ways of reversing visual system changes that have already occurred as a result of impaired early visual input.

The present shortage and enormously increased cost of monkeys for this research poses a threat to the continuation of such studies. There is great need for increased domestic primate breeding. And, because there may be a difference in congenital strabismus as it occurs in humans and the type produced experimentally in newborn monkeys, the search must continue for animal models in which congenital strabismus occurs spontaneously.

Studies of strabismus and amblyopia in humans must also continue. For instance, the age of susceptibility to the affects of strabismus, the minimal period of visual deprivation which may result in amblyopia, and the effects of cataract and corneal disease and other causes of abnormal early visual experience need to be better defined. Such knowledge is essential before the optimal age for therapy can be determined. In order to develop definitive guidelines, clinical data from the entire ophthalmological community should be pooled and analyzed by a central agency.

Clearly, the important questions that need to be explored in animals will originate in the clinical laboratory. Further progress in this important field will be enhanced by close interaction between research oriented clinicians and basic scientists.

Disorders Affecting the Control of Eye Movements

Disorders affecting voluntary eye movements and the occurrence of involuntary eye movements of one or both eyes are among the most serious problems facing the clinician. In most cases, their cause is difficult to identify. Even when this is possible, the mechanism underlying disordered eye movements is either unknown or poorly understood.

Nystagmus, a relatively common condition associated with certain retinal and brain disorders, in which there are jerky, irregular eye movements, presents an extremely serious problem for the patient and may interfere with normal visual development.

Although certain oculomotor disorders can be treated with some success by surgery and possibly other means, other types, particularly those which affect both eyes, are much less amenable to therapy.

Accomplishments

Fortunately, considerable progress has recently been made in understanding the mechanisms which control eye movements. Advances have been rapid and promise not only continued progress, but also that this new basic knowledge may soon be applied to disorders of the human oculomotor system.

For example, this knowledge has already permitted a more accurate interpretation of several kinds of abnormal eye movements created by

neuromuscular disease. Scientists have gained valuable insights into the different types of eye muscle fibers and their roles in regulating eye movements. In fact, knowledge of muscle mechanics is now so well developed that it is reasonable to predict that eye muscle prostheses will be designed in the near future to help restore normal eye movement control to nystagmus sufferers.

Research in understanding how the six extraocular muscles of the eye cooperate with one another to hold the eye in any given position has led to a new way of describing and diagnosing strabismus. This may prove valuable in predicting the outcome of corrective surgery.

Great strides have been made recently in understanding natural eye movement control in monkeys. As a result, the broad outlines of a complete sensorimotor control system have been described for the first time in the oculomotor system, long before it has been demonstrated elsewhere in the central nervous system.

The clinical implications of this work are already beginning to appear, and it is now possible to predict what eye movement abnormalities are likely to occur after disruption of circuits at various points.

These findings not only can aid the physician by helping explain eye movement patterns that have previously been totally mysterious, but also emphasize the need for new oculomotor tests which will provide more reliable information for diagnostic purposes.

Research Needs and Approaches

Many questions remain to be answered concerning eye muscle control mechanisms. Knowledge in this area has advanced to the point where future progress will probably be made only through basic research aimed at resolving specific functional problems or by applied research utilizing recent advances to diagnose and repair eye movement disorders.

At present, the most promising means of correcting certain defects of eye motor control is by the selective use of drugs. Research on this subject is of great importance and is discussed later under Potential Applications of Neuropharmacology to Disorders of the Visual System.

In the meantime, great benefits will accrue from working out the normal operation and structure of the eye movement control system, for this will form a foundation of knowledge that is indispensible to the future treatment of human oculomotor disorders. For this purpose, studies in primates and humans are absolutely necessary.

One important problem in this field is the inadequate training of most clinical investigators in mathematical analysis of complex systems. Further progress depends upon the ability to incorporate new findings into mathematical models which are growing ever more complicated as they grow increasingly realistic and useful.

To deal with this problem, the National Eye Institute should promote the sound application of engineering analytical principles to the study of eye movement control. Scientific conferences, special courses, and research fellowships in this area should be promoted to familiarize clinical workers with recent developments in the field and to attract scientists with the appropriate training into the area. Special fellowships should be designed to enable interested new ophthalmologists and other vision scientists to obtain additional training in the mathematical techniques of systems theory. If, with NEI encouragement, the lag time between the training of new interdisciplinary scientists and when they can contribute significantly to this field could be reduced, this would significantly accelerate progress in a field already in a rapid state of growth. Likewise, every effort should

be made to encourage the interaction of basic scientists with neurophthalmologists in order to bridge the gap between research and the pressing needs of the clinic.

Optical and Pupillary Disorders

Optical and refractive errors are by far the most common eye conditions, and although in the great majority of cases they can be readily treated with eyeglasses or contact lenses, understanding of their cause is far from satisfactory. This is particularly true of so-called malignant myopia in which the risk of blindness is considerable. Research into the cause and prevention of these and similar disorders must be a high priority for the National Eye Institute. The development of appropriate animal models—especially primates—is likely to yield the most fruitful results. (Research needs and opportunities in this field are discussed in the reports of the *Retinal and Choroidal Diseases* and *Corneal Diseases* Panels.)

Visual Sensory and Perceptual Disorders

An understanding of the basic mechanisms involved in normal vision is an essential first step to progress in the prevention, diagnosis, and treatment of all sensory or perceptual disorders. No "direct assault" on specific disorders in this field can substitute for the long-term benefit that is to be derived from fundamental scientific studies.

Neural Mechanisms

The partial unraveling of how visual information is processed at each neural level from the retinal photoreceptors to the visual "association areas" of the cerebral cortex of the brain is one of the most remarkable developments in neural science in the past two decades. That much of this work is now supported by the National Eye Institute is appropriate.

Furthermore, it is evident that research in normal vision continues to attract the most able investigators in neurobiology. It is noteworthy that in 1967 the Nobel Prize in Physiology or Medicine was shared by three scientists (Wald, Granit, and Hartline) whose work was in this area.

Research opportunities in this field were covered in the Council's first report, and the excellent work now being done should continue to be supported. In addition, the Council believes that research in the following area should be given special emphasis because of its potential application to disease problems.

Potential Applications of Neuropharmacology to Disorders of the Visual System

One of the major obstacles to the effective treatment of many visual disorders is the fact that, once damaged, human central nervous system tissue cannot be repaired. Until this impediment can be overcome, the only prospect for effectively dealing with central nervous disorders affecting vision will be through drug treatment. But, even before this can be accomplished, much more must be learned about the chemical substances (neurotransmitters) involved in the transmission of information from the retina to the visual areas of the brain.

Accomplishments

Neurotransmitters known to inhibit certain responses of neural cells have recently been used to test the idea that much of the selective responses of visual nerve cells to specific visual patterns is determined by specific inhibitory connections. For example, a cell in the visual cortex which responds only to a moving, precisely-oriented bar of light of a specific length can be made to respond to a longer bar, without changing the requirements for its orientation or direction, by chemically interfering with the effect of the neurotransmitter which normally controls the cell's response.

In addition to providing new insights into the "wiring diagrams" underlying visual cells' sophisticated response patterns, such studies are already leading to new insights into how visual field defects and loss of vision from amblyopia could possibly be reversed by surgery and the use of drugs.

Research Needs and Approaches

Such studies in the developing visual system may be particularly fruitful because early visual experience appears to increase the nerve cells' selectivity for particular visual patterns, and this selectivity is often determined by inhibitory mechanisms.

Of great interest is research to explore the possibility of establishing a neuropharmacological basis for the regulation of "plasticity" in the visual cortex of the brain. This could be of great importance to rehabilitation of visually impaired people, for it could lead to means of utilizing alternative pathways for the transmission of visual information in cases where normal channels have been damaged by disease or injury.

Progress toward the development of such therapy will be slow, and more basic studies are needed to determine whether or not there are real possibilities for specific pharmacological treatment of visual nervous system disorders.

Psychophysical Functions

Application of Visual Psychophysical Techniques To Clinical Diagnosis of Visual Disorders

The investigation of vision by procedures which measure psychological or behavioral responses to physical stimuli continues to be one of the most valuable tools in vision research. It is now time to attempt application of these techniques to the clinical diagnosis of visual disorders. Research in this area is expected to provide a whole new range of diagnostic tools for the clinician.

Accomplishments

A variety of nonintrusive techniques have been developed for the study of normal visual function. These include methods which make it possible to differentiate the roles of different types of receptor cells in the retina as well as discriminate among neural and photochemical mechanisms of the living eye. Such tests may be extremely useful for early diagnosis of diseases which may selectively influence these various receptors or mechanisms.

Perhaps the most significant aspect of vision is its capacity for spatial resolution, that is, the separation of elements in a visual pattern. This is commonly measured in terms of visual acuity or sharpness. However, normal vision involves many other discriminations of contrast and spatial patterns. Several tests have been devised to study the various mechanisms believed to underly these processes, and many can discriminate retinal from more central neural mechanisms. Other tests can measure the ability to detect the duration of a light stimulus. In spite of these developments, little has been done to apply such tests to the clinical diagnosis of visual disorders.

Among the oldest and best established of the clinical applications of psychophysical testing are the several tests of color vision. However, these tests were designed for the assessment of congenital color perception defects; very little effort has been made to relate acquired color vision defects to the disease processes or toxic affects of a variety of drugs which cause them.

Research Needs and Approaches

Ultimately, it is hoped that psychophysical testing in a clinical setting will make it possible to pinpoint the location of visual malfunctions in such structures as the outer segments of the rod and cone photoreceptor cells or in particular groups of optic nerve fibers.

Before this can be done, research is critically needed to determine whether any of the existing visual function tests can be used in the differential diagnosis of retinal and sensorimotor diseases. This will require a joint effort on the part of seasoned clinicians and well-trained psychophysicists.

Specific tests may be able to predict susceptibility to certain diseases. Given such an indicator, appropriate specific treatment could be initiated at a much earlier stage of the disease than is now possible. This may have considerable implications for the high-risk patient.

In order to encourage the application of psychophysical and electrophysiological procedures in ophthalmic diagnosis, special workshops and joint research projects involving basic and clinical investigators should be promoted. (One such workshop sponsored by the NEI was held in September 1976.) In addition, special training fellowships should be offered to enable interested clinicians to learn first hand the essential techniques of psychophysical testing. Comparable opportunities should be provided for interested psychophysicists to spend time in the clinical setting learning the special needs of clinical practice.

Electrophysiological Techniques Applicable to Man

Because it is usually not possible to use invasive electrophysiological techniques in human studies, there is considerable interest in developing new methods and refining existing ones for clinical electrophysiological studies.

The usefulness of the electroretinogram (ERG), in which contact lens electrodes are placed on the surface of the eye, has been greatly enhanced by technological developments. One noteworthy development is the ability to isolate responses from the photoreceptors themselves as distinct from responses from retinal neural cells. These developments have immediate application to the diagnosis of human retinal disorders.

Records of electrical activity from the visual centers of the brain can also be made. Technological improvements in obtaining visually evoked responses (VER) have increased the usefulness of this method as well. This has made it possible to obtain evidence about the normal or pathological function of certain areas within the visual processing centers of the brain.

Of particular clinical importance are new methods for studying visual function in human infants. Not only is it possible to record ERG's and VER's, but there are also new behavioral measures that depend on observations of infant eye movements. These have made it possible to measure visual acuity, color vision, and eye movement control in infants less than six months of age. Using these techniques, it should be possible to detect disorders such as strabismus and amblyopia at a much earlier age and to initiate appropriate treatment sooner.

Sensory and Motor Disorders Related to Specific Disease Processes

Many diseases affecting the central visual pathways are of a general nature and not specifically related to the visual system. As such, these disorders do not generally come within the province of the National Eye Institute. Because many are being actively investigated by other components of the National Institutes of Health, only where their relationship to the eye or visual system is of paramount importance should their investigation be considered for support by the National Eye Institute.

Rehabilitation

The Panel recognizes rehabilitation of both the blind and the partially sighted as a subject of considerable importance. But, because this subject applies to visual disability from all causes, not just sensorimotor disorders, it deserves greater prominence in the overall program of the National Eye Institute. The Panel therefore recommends that the National Eye Institute consider establishing a separate program for visual rehabilitation in which a strong effort could be made to promote the scientific study of prosthetic or other mechanisms that may benefit the visually handicapped.

Although much work is being done by many other governmental and private agencies to improve the quality of life, mobility, and communicative capacity of those with visual impairments, the National Eye Institute is, and should remain, the principal source of support for fundamental scientific work in this important area.

Vision Research Training

Introduction

Vision research training is an essential component of the national policy of fostering improved prevention, diagnosis, and treatment of blinding and disabling eye diseases. The *Vision Research Training* Panel considered the existing NEI training program, including its record, and reviewed factors impinging upon or potentially affecting its future development. Based on this assessment, a number of recommendations to the National Advisory Eye Council were formulated.

Current Vision Research Training Programs

Within the limits of legislative and executive authority, the National Eye Institute has responded to vision research manpower needs by providing opportunities for training individuals in the research laboratories of established investigators and by promoting the development and maintenance of centers of vision research that use multidiscipline approaches in investigating important eye and visual system problems.

The current research training authority of the NEI is derived from Title I of Public Law 93-348, the National Research Act, enacted in 1974. This Act authorizes individual postdoctoral research fellowship and institutional fellowship awards; the latter may have a predoctoral component.

Individual Awards

A variety of mechanisms exist for assisting the advancement of individuals at different levels of research development. Predoctoral training is supported only through institutional training grants. Postdoctoral support is provided through both institutional training awards and individual fellowship awards under the *National Research Service Awards* program. These awards are made to qualified young scientists who seek additional in depth training for a period up to three years following the receipt of a doctoral degree.

Academic Investigator Awards are designed to help an individual become established as an independent investigator, usually in an academic setting.

About five *Research Career Development Awards* are granted each year to individuals who have established reputations as highly promising independent investigators.

The NEI also offers a *Special Visual Sciences Research Award* program which is designed to provide research support for newly trained investigators who completed their training not more than five years prior to the beginning date of the proposed project. This award is intended to give young investigators an opportunity to develop new concepts and techniques and to obtain preliminary research results which may be of value in preparing a regular research grant application. Direct costs are currently limited to $10,000 per year for three years, and funds may not be expended for the salary of the principal investigator. The review process is the same as for regular research grants, and there is no special allotment of funds for this type of grant.

Institutional Awards

Before the National Eye Institute and its progenitor, the National Institute of Neurological Diseases and Blindness, were established, only a few groups in the United States were organized for research in vision. Most vision research was conducted by individuals who were isolated in academic departments concerned with a specific research discipline. In most medical schools, ophthalmology was either organized as a division of the department of surgery or was not recognized as an organizational unit at all. Similarly, most schools of optometry were not prepared to meet the demand for research. Therefore, when the NINDB was established, institutional grants were used to assist in "establishing, expanding, or improving training opportunities."

Graduate Training Grants related to vision and disorders of the visual system were first made in 1954. At the time the NEI began operation in 1970, 61 were still active. After 1977, only 12 grants will be active, and the program will be completely phased out by June 1979. These grants were provided "to improve the institutional environment in which the proposed research training is conducted and to enable the institution to pay subsistence stipends and allowances to fulltime trainees in order that they may participate in the (training) program." They can therefore be considered the first phase in the process of creating centers for vision research.

After the establishment of units or departments of ophthalmology, each with a small core of full-time investigators, individuals successfully competed for research project grants. Once this base was established, more comprehensive training and development of new investigators in vision research could begin.

Many recipients of the Graduate Training Grant have noted in their annual progress reports that the receipt of such grants was a major contributing factor in achieving departmental status for their ophthalmology units. More specific information comes from the heads of 40 of the 54 ophthalmology units that have been awarded training grants. Eighteen of these units became departments coincident with or subsequent to the receipt of the training grant. During the period of time that the grants were in effect, the average number of full-time faculty increased from two to ten. The average number of research project grants received increased from less than one to six.

Institutional National Research Service Awards, instituted in 1975, are similar to traditional training grants in that the recipient institution is responsible for the selection of predoctoral and/or postdoctoral fellows. Support is available not only for stipends but also for maintaining and upgrading the research environment. The intent of this award is to encourage work in selected priority disciplines as determined by the National Advisory Eye Council.

In addition to training grants, the National Eye Institute provides support to established research groups through *Research Center (Core) Grants* and *Specialized Clinical Research Center Grants.* Core Center Grants support shared resources or facilities that are needed by a group of established investigators. To be eligible for core support, a research group must already have several active research project grants from the National Eye Institute. Specialized Clinical Research Center Grants are designed to facilitate application of scientific methods to clinical outpatient research on a specific disease or problem. Awards are made to established units that demonstrate that they have the necessary competence and facilities to carry out the proposed program.

Both of these awards contribute to the quality of the institutional research environment and thus enhance opportunities for excellence in vision research training.

Factors Affecting Training Programs

The National Research Act of 1974 provided for a national study to establish the qualitiative and quantitative needs for biomedical and behavioral research personnel, to assess current research training programs, and to determine modifications that may be required. The National Academy of Sciences conducted such a study for the Department of Health, Education, and Welfare and submitted a report to the Secretary in May 1976. Comments and recommendations contained in that document which are pertinent to this report may be found in the Appendix to the unabridged *Vision Research Training* Panel report in Volume Two of this plan.

Opportunities for Research

In considering the need for training programs, one must consider whether research opportunities and positions will be available for newly trained investigators. This, in turn, depends upon the availability of financial resources. If current trends continue, it is reasonable to expect increases in federal support to the extent that resources for research will at least keep pace with inflation. However, there may be shifts in priority among the various areas of federal health spending.

University departments outside medical schools are not expected to expand significantly in the immediate future; the opportunities for research in vision will depend on the particular interests of individual faculty members and on the availability of research support.

By contrast, the faculties of health professional schools are likely to expand in coming years as a result of increased demands for physicians and other health care personnel, decreased immigration of foreign medical graduates, and increased university responsibility for graduate and continuing professional education. Clinical research on the visual system will be largely vested in departments of ophthalmology and schools of optometry. Training grants, research project support, faculty practice plans, specialization, and other factors have led to the development of many strong institutional units. As these units increase in number, there will be an accompanying increased need for trained clinical scientists.

Areas Needing More Research

The need for biomedical research training in any given discipline is related to the importance of the disease problem(s) to which it is relevant and the degree to which the results of training can be applied when required. The National Eye Institute has categorized vision research into five programs. A rating can be given to each of these in terms of its prevalence as a health problem, and this can be compared to the relative expenditure for research and research training in each program. (For details, see Tables 8 and 9 in the unabridged *Vision Research Training* Panel report in Volume Two of this plan.) However, rather than paralleling the prevalence of the disorders addressed by the program, the relative support for each NEI program actually coincides with the relative distribution of grant applications the Institute receives, itself a measure of scientific interest and opportunity. (See Table 10 in the *Vision Research Training* Panel report in Volume Two.)

The ultimate prevention of visual disorders depends upon a more complete understanding of basic processes—normal structure, growth, development, and health maintenance—as well as factors that alter these processes such as aging, trauma, infections, nutrition, environment, drugs, genetics, and neoplasms. The state of knowledge at this time suggests that long-term advances depend on vision research and research training which are built on fundamental disciplines such as biochemistry, physiology, pathology, immunology, microbiology, and anatomy. The importance of basic research of this type to clinical advances and new forms of treatment has been well documented.

Recommendations

The research training programs of the National Eye Institute have had a profound effect on the Nation's capacity to conduct research on vision and its disorders. The number of qualified individuals and organized units actively engaged in vision research has been greatly increased through the programs NIH has supported during the last two decades. DHEW biomedical research training programs were reevaluated by the Office of Management and Budget a short time ago, and in 1975 the Congress enacted new training legislation which necessitated the issuance of new guidelines by NIH. Graduate Training Grants, which were instrumental in the organization of research groups and departments of ophthalmology, and Special Research Fellowships, which supported advanced clinical and clinical research training, were discontinued as a result of the new legislation. The National Eye Institute's own training guidelines placed greater emphasis on the development of individuals who would have lifelong careers in vision research.

It is still too early to evaluate the full effects of the new course that was set, but in considering possible recommendations for the future of National Eye Institute vision research training support, there are nine worthy of mention. The first four are in line with current practice and are listed as a reminder of their importance. The last five call for adjustments in present training policy to meet perceived needs.

Need for Excellence

The National Academy of Sciences has been given the continuing responsibility to study the personnel needs of biomedical and behavioral research, and its recommendations will serve as guidelines for the implementation of the National Research Act of 1974. The training policies of the National Eye Institute have been in accord with and, in fact, have anticipated the recommendations of the Academy. The Academy, like the National Eye Institute, emphasizes the need to sustain the quality of the research environment to improve the chances that efforts will be directed toward research that will result in major advances against disease and disability.

Need for Stable, Consistent Policy

As a result of National Eye Institute training programs, departments and sections of ophthalmology, schools and colleges of optometry, and other academic centers throughout the United States have developed or strengthened

their research components so that multidiscipline groups with active programs now exist. These groups are generally small, and the stability of their newly acquired capacity for research depends on the continuity of support for vision research and training. A consistent policy for vision research training which is systematically regulated is essential to maintaining the gains that have been made. The National Academy of Sciences supports this concept, and it is reflected in the National Eye Institute's orderly introduction of the National Research Service Awards and phasing out of the types of awards that they supersede.

Need for Vision Research and Training in the Basic Sciences

At the present time, most of the Institutional National Research Service Awards are made to departments or groups involved in basic research. This is largely because the terms prescribed for predoctoral and postdoctoral fellowships coincide with practices and stipends in basic science departments. Vision research benefits from the interest that is generated in these departments. First, the number of vision investigators is increased. Second, the discipline-oriented environment may suggest concepts and approaches that are less likely in a clinical setting. Third, predoctoral programs of graduate schools are conducted in basic science departments—the place and time at which the research interests of future faculty members are frequently determined.

Need for Training in a Clinical Setting

Institutional National Research Service Awards that are administered by a clinical department with a complement of established investigators are most useful in providing particular types of training. For individuals with Ph.D. degrees who are interested in vision research, the clinical setting offers an excellent base in which to become acquainted with a broad, multidiscipline field. For individuals with professional clinical training who are interested in academic careers, postdoctoral fellowships offer a means of learning the methods and approaches of biomedical research. For individuals at a predoctoral level who have an interest in medical research, a clinical department with faculty members who hold joint appointments in a graduate school offers an exciting setting in which to meet their research requirements.

Need for Clinical Investigators

The greatest need for new vision research personnel is in clinical research. Clinicians are continually challenged and stimulated by the problems they observe in patients. If, in addition to being clinicians, individuals are also well-trained investigators, the likelihood of having research directed toward the solution of patient problems is increased. There is a great need for advanced clinical research training in specific areas where clinical problems can be delineated and where attention can be paid to the development and evaluation of new methods of diagnosis and treatment.

Doctoral programs in the professional schools are generally directed toward producing clinicians rather than research scientists. Therefore, it is important to support postdoctoral training of clinicians who are willing to spend at least one year, and preferably two, in either a basic science department or a well-staffed clinical department in which clinical problems related to vision are investigated in association with basic scientists working on analogous problems.

National Research Service Awards, for individuals who have just received a doctoral degree, and Academic Investigator Awards, for individuals who have completed the formal requirements of a residency, are the training mechanisms of choice for this type of training. The number of Academic Investigator Awards should be increased from the current limit of six per year, and the limitation of one award per institution should be removed. Successful awardees should look forward to future support through Research Career Development Awards or regular research project grants. In addition, because existing training programs do not adequately accommodate the full range of clinically-oriented candidates, the Panel recommends that a detailed proposal for training clinical investigators be prepared by the NEI staff and submitted to the National Advisory Eye Council for consideration.

Need for Individual Fellowships

The processing of applications for Individual National Research Service Awards should be modified to expedite the commitment of these awards. Reviews should be made several times each year, and a system of advanced funding should be established so that monies are assured for all approved applications that are scheduled to be funded.

Need for Initial Research Support for New Investigators

The National Eye Institute offers Special Visual Sciences Research Awards to attract and support young investigators. At present, there are few applications for this special award, and the concept of assisting young investigators with modest start-up grants is not being served.

The Panel recommends adding to the present award base of $10,000 a professional salary component not to exceed $15,000. The Panel also believes that it is very important for the NEI to inform the NIH Study Sections as well as potential applicants of the purpose of Special Visual Sciences Research Awards. Finally, applications for this award should not compete directly with regular project grants in NEI funding decisions.

Need to Consider Program Emphasis

Support for research and training related to the prevention of disease warrants greater emphasis. This requires a basic understanding of normal biological as well as pathological processes and suggests a need for training and supporting basic scientists who are interested in and qualified to work in vision research. Research and training programs that will lead to the prevention of disorders of vision should therefore be given high priority.

Need for a New Administrative Arrangement

Until recently, research and training priorities in vision research seemed to correlate better with the research interests of investigators, as indicated by the type and volume of grant applications received, rather than with priorities that have been defined as public policy. However, broad national research policy must be established by blending the perceived interests of the American public with the

scientific knowledge and judgment of experienced investigators. This is accomplished in part through program advisory groups, such as the National Advisory Eye Council, which include representatives of the scientific and practitioner communities as well as the general public.

The Panel recognizes that needs for research training will vary according to the direction of scientific advance and the availability of funds. Optimal results can be obtained if all resources for training are in effect pooled; if a quantitative five-year program plan that is updated each year projects the allocation of funds among different types of training programs and among the five major fields of research that are supported by the National Eye Institute; and if, pending the adoption of a more unified approach to training, the staff of the National Eye Institute is encouraged to modify training guidelines and seek applications in accord with established research priorities.

Training Needs for 1978-1980

The National Advisory Eye Council asked each of the five research program planning Panels to estimate the number of new principal investigators that will be required during the period 1978-1980 to undertake the priority projects they have recommended. These estimates are presented in the first column of Table 1 and are further broken down by subprogram in the tables following each unabridged research Panel report in Volume Two.

It is important to emphasize that in making these estimates, the Panels considered not only the need for newly trained investigators, but the likelihood that established scientists presently working in other fields of research could be attracted to working on related problems in vision. Furthermore, the Panels took into account the fact that there now exist many experienced younger investigators who would be capable of assuming principal investigator positions during this period.

It was one of the responsibilities of the *Vision Research Training* Panel to determine how many of these additional principal investigators will have to be newly trained and to present estimates of future budget requirements for vision research training and career development awards. The *Vision Research Training* Panel's estimates of the need for newly trained investigators are presented in the second column of Table 1 and are based on four premises:

1. There will be a continuing need to support the development of vision research personnel inasmuch as (a) there are, as documented in this report, a wealth of opportunities in vision research that promise major advances against the leading causes of blindness and visual impairment, (b) new research techniques and instruments continue to be developed which create a demand for new knowledge and skill, and (c) research in vision is enhanced if individuals initially qualified in either a basic science or in a clinical field obtain additional experience in the other environment.

2. Ninety-six percent of vision research in the United States is federally funded. Of this amount, the National Eye Institute supports 73 percent. Research training support by the NEI should be commensurate with its overall support of the field of vision research.

3. In the past few years, a cadre of competent investigators has been trained to meet many of the demands of vision research; therefore, it is possible to decrease somewhat the rate of growth for training support in the 1978-1980 period and in subsequent years.

4. There is a certain amount of mobility of scientists among related fields of interest. Vision research should continue to benefit from this mobility. Therefore, it is not necessary to budget for training the total number of required individuals.

Based on an assessment of existing manpower in the various areas of vision research, the realistic likelihood that a certain number of investigators from other fields will enter vision research, and the expected availability of funds, the Panel proposes that the Council budget for 1978 provide for an additional 23 career type training awardees and an additional 115 fellows and trainees for programs that last an average of two to three years. Thus, provision is made for training only about 23 percent of the total need for new principal investigators during the period 1978-1980.

Training needs vary with the specific plans for individual NEI programs. *Retinal and Choroidal Diseases*, for example, which represents 48 percent of the projected FY 1978 research funds (research grants, contracts, and centers), is judged to require only about 36 percent of the training and career development funds because a large portion of the research dollars in this program is designated for multi-center clinical trials. Such trials draw in great part upon existing staff of academic institutions, many of whom are not otherwise directly involved in research.

Table 1

Vision Research Training Needs
1978-1980

	New Principal Investigators	Newly Trained Investigators
Retinal and Choroidal Diseases	208	49
Corneal Diseases	100	21
Cataract	46	8
Glaucoma	54	14
Sensory and Motor Disorders of Vision	192	46
TOTAL	600	138

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Vision Research and Biomedical Science

IMPORTANT AS THEY are in their own right, disorders of the visual system should be looked at neither in isolation from other diseases and disabilities nor outside the context of the rest of biomedical science. Ocular complications—often extremely serious ones—accompany many systemic afflictions. For example, 30 percent of all genetic diseases have ocular manifestations. Equally important, there are many instances where insights can be gained into normal and pathological processes operating throughout the body by studying events occurring within the eye. In this chapter, the substantive interactions between the programs of the National Eye Institute and four major areas of current interest in biomedicine generally are summarized.

Diabetes

Research focused on diabetes mellitus and its complications is of great interest to many components of NIH as well as to other governmental, professional, and voluntary health organizations. Of particular concern to the National Eye Institute are the abnormal changes in retinal blood vessels and other ocular structures that accompany this disease. For example, diabetic retinopathy has emerged within the past decade as one of the leading causes of new blindness in the United States.

As described in the preceding chapter, the NEI conducts and supports a broad-based research program involving many facets of the ocular complications of diabetes. Studies range from laboratory investigations of the metabolism of the cells which line the capillaries of the retina to multicenter clinical trials of new surgical procedures and other treatments. It is especially noteworthy that the NEI's clinical trial of photocoagulation therapy for diabetic retinopathy was singled out by the National Commission on Diabetes as "an excellent example of a carefully executed and controlled clinical trial yielding results of significance in the clinical management of diabetes."*

The NEI and the vision research community strive continuously to ensure that research on the ocular complications of diabetes will both gain from and

* *The Long-Range Plan to Combat Diabetes, 1976 Update.* Report of the National Commission on Diabetes to the Congress of the United States. US DHEW Publ No (NIH) 77-1229, Washington, DC, 1977.

contribute to advances in other aspects of diabetes-related research. For example, the finding that in diabetes the blood may be more viscous than normal not only offers a clue to the etiology of diabetic retinopathy and other disorders of ocular blood vessels, but also provides a basis for exploring the effects of aspirin and possibly other inhibitors of blood platelet aggregation on the course of abnormal retinal changes. Conversely, by capitalizing on the relative ease with which the normal and pathologic retinal circulation can be studied, vision scientists are contributing new knowledge about capillaries and other small blood vessels which should be relevant to microvascular disorders in other organs such as the kidney.

The NEI staff helps to further the already close interaction among vision scientists and the diabetes research community by participating actively in the National Diabetes Advisory Board, the Diabetes Mellitus Coordinating Committee, and other governmental activities designed to promote a comprehensive, integrated approach to the problem of diabetes. The NEI's role in diabetes research is noted explicitly in the National Diabetes Mellitus Research and Education Act of 1974 and the Arthritis, Diabetes, and Degenerative Diseases Amendments of 1976. In addition, the NEI staff works directly with professional and voluntary organizations such as the American Diabetes Association, the Juvenile Diabetes Foundation, and the Pennsylvania Diabetes Association which have an active interest in all matters pertaining to the care of diabetic patients. The progress that has been made in this area and the current research emphasis on the ocular aspects of diabetes indicate both the importance of the problem and the responsiveness of the vision research community to issues of broad social concern.

Neurobiology

One of the most exciting and promising areas in biomedical science in terms of the pace of advance and the potential payoff for patient care is the biology of the nervous system. Neuronal "wiring diagrams" are being described in ever greater detail, functional interrelationships between neural structures are becoming increasingly better understood, and the detailed mechanisms of electrical and chemical transmission of neural signals are being probed in ways that could only be dreamed of a few years ago. Clearly, emerging concepts about the structure and function of the nervous system will have a profound influence on the diagnosis, treatment, and prevention of a host of human disorders.

The special characteristics of the visual system have contributed much to the coming of age of neurobiology and should continue to do so for the foreseeable future. Because the eye offers a sensory channel whose inputs can be controlled with exquisite precision, because the retina and optic nerve terminals are the most accessible portions of the nervous system, and because most of the higher nervous centers which subserve vision are well identified, many neurobiologists have been attracted to the visual system as a productive arena for their explorations. For example, experiments in which newborn animals are deprived of visual stimuli for various lengths of time demonstrate how profoundly sensitive the development of the nervous system is to the nature and scope of early sensory experience. These experiments provide a wealth of information about how the visual nervous system is organized to carry out the information processing tasks that underlie the sensation of sight. Moreover, these findings concerning the effects of early visual deprivation in animals are influencing management of the human patients. Ophthalmologists, optometrists, pediatricians, and others who care for children with ocular disorders are becoming

increasingly sensitive to the importance of providing these youngsters with as nearly normal a visual experience as possible and thus preventing—or at least reducing the extent of—abnormal development of the visual nervous system and attendant amblyopia.

Genetics

The role of heredity in human disease has emerged within the past two decades as one of the most important areas of inquiry in biomedicine. As more and more disorders come to be understood in terms of the inherited structural or functional deficits that give rise to their clinical manifestations, opportunities emerge for improved diagnosis and treatment of afflicted individuals, identification of carriers, and prevention of disease through genetic counseling.

There are now more than 2,000 known genetic disorders in man. Ocular complications occur in an estimated 30 percent, and in about one-half of these, the eye is thought to be the only organ system affected. Thus, hereditary disorders of the visual system such as retinitis pigmentosa are appropriately included as important areas for research and, it is hoped, are among the human afflictions that one day will be eliminated as a result of studies based on genetics concepts and methods.

As in the case of diabetes, members of the vision research community are in the mainstream of research in genetic diseases. The NEI complements this involvement by its participation in such groups as the DHEW Interagency Genetics Coordinating Work Group which was created by the Health Research and Health Services Amendments of 1976. In addition, the NEI cooperates with private organizations such as the National Retinitis Pigmentosa Foundation, Inc., which do much to promote research, treatment, and education related to hereditary disorders that affect the eye.

Nutrition

In recent years, the relationship of nutritional status to the etiology and pathogenesis of a variety of human disorders has become the focus of considerable national attention. Even in highly developed societies such as the United States where food is plentiful and readily available to the vast majority of the population, and general malnutrition rarely occurs, there clearly is much to be learned and applied concerning dietary habits and their consequences relative to various systemic and organ-specific disorders. In recognition of this, the NIH has created a Nutrition Coordinating Committee to promote interchange of information among its various organizational components whose programs involve nutrition and to insure that the NIH-wide program on nutrition research is both comprehensive and well-integrated. The National Eye Institute is represented on this coordinating committee.

Of particular interest to the NEI is the role of vitamin A in the development and functioning of the retina and cornea. The NEI's research interests include not only the role of vitamin A in normal ocular physiology but also how it relates to the blinding condition keratomalacia that is so prevalent in Central America, the South Pacific, the Indian subcontinent, and in other parts of the world. As research produces more knowledge about how vitamin A is handled in the protein/calorie deficient child and others who have been subjected to inadequate diets, it should be possible to design and evaluate—first in a clinical situation and ultimately under field test conditions—new approaches to vitamin

A and protein supplementation that may prevent or at least reduce the severity of nutritional blindness. Toward this end, the NEI is actively collaborating with other governmental agencies as well as the International Agency for the Prevention of Blindness, Helen Keller International, the World Health Organization and its affiliates, and other groups which are committed to improving public health throughout the world.

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Program and Management Issues

IN THIS CHAPTER, the Council highlights a number of scientific and management issues of importance to this national plan. Some of these are topics introduced in Chapter 2 that are related to implementation of the Council's recommendations. Others concern problems and needs common to all of the National Eye Institute's programs. Specifically, this chapter focuses on clinical vision research and how best to encourage and support it, the National Eye Institute's concept of vision research centers, the need for additional animal models of human eye diseases, scientific disciplines of importance to all vision research, and the role NEI should play in fostering the transfer of new vision research knowledge into the health care milieu.

Support of Clinical Research

Clinical research in vision encompasses all scientific investigations in which the visual system of humans is the object of study. Thus, using this definition, clinical research may be said to include studies of the healthy eye as well as studies intended to clarify the etiology or pathogenesis of visual disorders; achieve better diagnosis, treatment, and prevention of them; and improve capabilities for rehabilitating those afflicted with irremedial visual deficits.

High quality ocular clinical research embodies the same principles and approaches as other areas of basic and applied science. Clinical investigators first identify a problem of interest and formulate a hypothesis relative to the potential resolution of that problem. Then, they design and conduct investigations to provide definitive tests for the stated hypothesis. Finally, they evaluate their findings in relation to the original hypothesis and its alternatives.

The types of investigations performed by clinical scientists include evaluation of individual case histories, retrospective analyses of data culled from standard clinical records, correlational studies which might uncover predictive relationships, studies of the natural history of disease, and controlled experimental studies which might furnish definitive information about causal relationships or the relative safety and efficacy of alternative therapies. Prospective, controlled, experimental studies, as a class, are called clinical trials. The National Institutes

of Health defines a clinical trial as "a prospective research activity undertaken to assess the effect and value of prophylactic, diagnostic or therapeutic agents, devices, regimens, procedures, etc., in human subjects."*

Whatever type of investigation he or she decides to conduct, the clinical investigator faces a number of formidable issues which are either absent or much more readily resolved when one is performing laboratory research. Some examples are:

- Resolving numerous ethical concerns prior to initiating studies with humans;
- Developing and maintaining administrative arrangements for identifying prospective participants in a study and for following those who are eligible and elect to enroll;
- Developing understandable and accurate information materials about the objectives of and procedures associated with the study so that participants may give appropriately informed consent;
- Bringing to the clinical setting concepts and resources which have been demonstrated to be effective in the laboratory environment or in nonclinical disciplines;
- When sample size projections indicate that an adequate number of patients is not available to a single group of investigators, bringing together in a cohesive and standardized fashion the resources of a number of geographically separated institutions.

The National Eye Institute recognizes the need for providing resources to the vision research community for the development and conduct of clinical research projects, especially clinical trials, and employs several types of awards for this purpose. In particular, the NEI supports clinical studies by means of the research project grant, the research contract, and the specialized clinical research center grant.

In all cases, the NEI emphasizes the importance of carefully defining certain aspects of clinical research projects before patients are subjected to experimental interventions (if any) and observations. Paramount among these are:

- Design of the study and the method for assigning patients to each of various experimental conditions;
- Procedures for reducing investigator bias (masking techniques);
- Criteria for including or excluding patients;
- Criteria for terminating the study;
- Statistical techniques that will be used in evaluating the results of the study.

In addition, where alternative treatments are to be compared, investigators are urged to restrict themselves to those instances where, based on knowledge currently available, the estimated benefits and risks of the new intervention(s) to be studied are comparable to the potential benefits and risks of the conventional therapy or, where no established therapy is available, to the potential benefits and risks of allowing the disorder to take its natural course. By adopting this approach and then randomly assigning participants to the experimental groups, the investigator not only achieves scientific rigor but also attains

* *NIH Inventory of Clinical Trials, Fiscal Year 1975, Vol I.* Research Analysis and Evaluation Branch, Division of Research Grants, NIH, Bethesda, MD, p iii.

a high ethical standard because every participant has the same chance of receiving whichever of the therapies is eventually found to be best.

Research Project Grants

The NEI has always been receptive to project grant applications for clinical research and will continue to be so. In the past year, in response to the high level of interest within the vision research community in clinical trials, the Institute augmented its procedures for reviewing and awarding individual clinical research project grants. Now, whenever NEI advisors and staff identify a grant application for a proposed clinical trial that satisfactorily outlines the objectives of the study, clinical significance of the problem addressed, scientific background, and the technical feasibility of the proposed approach but lacks a comprehensive and detailed account of procedures for conducting the study (a manual of operations), the Institute considers awarding a grant expressly for developing and testing such a document. Once a manual of operations has been completed and judged acceptable by NEI advisors, the funds required for the execution of the study can be determined and made available via the original grant in accordance with normal NIH procedures. When preliminary work demonstrates that a multiclinic study is required, the original applicants and their potential collaborators at other institutions are encouraged to submit a coordinated set of new grant applications requesting and justifying funds to carry out the study. Because multiclinic trials generally are significantly more complex and costly than single-clinic trials, the results of this "second pass" through the NIH grants peer review system are invaluable in helping NEI staff determine whether or not to fund the study.

These administrative practices should help promote high quality grant-supported clinical trials of many aspects of eye care. Among the studies now being pursued in this way are a controlled trial of orthokeratology (the use of contact lenses to change the curvature of the cornea in order to reduce myopia); evaluations of laser treatment for retinal branch vein occlusion, macular edema, and shortening the duration of central serous retinopathy; and a determination of the role of vitamin E in reducing retrolental fibroplasia (oxygen-induced blindness) in premature infants.

Research Contracts

The NEI considers the research contract the best way of supporting clinical research when all of the following apply: (a) the topic is one of considerable national importance; (b) NEI staff members and their advisors play a role in developing the concept and design of the study; (c) the performance of the study requires the collaboration of a number of institutions or clinics; and (d) the NEI has the staff resources to assume responsibility for the management as well as the sponsorship of the study.

The bulk of NEI's research contract funds are committed to the support of cooperative clinical trials of new therapies for diabetic retinopathy. Other clinical studies which the NEI is supporting under contract include projects to develop new surgical techniques for glaucoma, improve photographic techniques in fluorescein angiography, and evaluate retinal and choroidal circulation. The Institute has also awarded a contract for the biostatistical assessment of existing data on the safety and efficacy of artificial lens implants.

Specialized Clinical Research Center Grants

The specialized clinical research center grant is an award which provides support both for a number of individual projects involving human subjects or human tissue and for supporting research resources. A specialized clinical research center is viewed as a unique environment in which important and definitive clinical research employing the latest methods is conducted on a particular human eye problem. The types of projects conducted would not, as a rule, be practical outside the center. The NEI utilizes this funding mechanism only under exceptional, clearly-defined circumstances.

Specialized clinical research centers are potentially an excellent mechanism to foster the search for pathological, biochemical, and physiological correlates of visual system disorders—especially those for which no generally accepted treatment exists. Clinical investigators need to identify relatively large groups of patients in specific disease categories and, along with the normal delivery of eye care services to these patients, do the following:

- Compile well-documented records of the course of disease, including responses to whatever standard therapies are used;
- Complement traditional clinical observations with selected visual function tests and other more research-oriented measurements that may provide some insights into the etiology or pathogenesis of the disorders involved;
- Make arrangements to obtain human tissues at the time of surgery and entire eyes following the death of patients in order to carry out the kinds of biochemical and pathological analyses that cannot be performed otherwise;

With the comprehensive data bases generated by the foregoing activities, clinical and laboratory investigators should have a wealth of new opportunities to test hypotheses about the underlying mechanisms of disease, the effects of standard treatments, and the prospects for new types of therapies.

Vision Research Centers: The National Eye Institute Concept

Until 1976, the National Eye Institute employed three large-grant mechanisms: the research program project grant, the core research center grant, and the specialized clinical research center grant. In contrast to the regular research project grant, which provides support for a discrete, specified, circumscribed project performed by a principal investigator and his or her own research team, these large grants usually provide support for broad-based, long-term programs of research. Generally, they are designed to bring together through common support the activities of a number of investigators and teams. However, the ways in which they do this, and the specific purposes of each, often differ considerably.

In 1973, the National Advisory Eye Council evaluated the three large-grant types with particular emphasis on the research program project grant. The Council noted that the research program project grant has certain advantages: it provides stable yet flexible research support for the investigators and institutions involved, and it brings together not only scientists with common vision research interests but also investigators from other disciplines who desire to apply their expertise to vision research problems.

The Council recognized, however, that these advantages were offset by the fact that collections of projects are inherently difficult to describe and review satisfactorily in the context of a single grant request. They almost inevitably will exhibit considerable heterogeneity in terms of the scientific quality of the work and its relevance to the NEI mission. But, most if not all of the program project's advantages, the Council further recognized, could also be provided by the core research center grant, especially if the principal eligibility criterion for receipt of a "core" grant were the existence of several, perhaps four, regular research project grants. Accordingly, the Council recommended that the National Eye Institute discontinue the use of research program project grants. In fiscal year 1977, the last of these supported by the NEI were phased out.

At present, the NEI has a small program of research center support. During FY 1976, there were ten core research centers receiving NEI support, and five specialized clinical research centers. Total center support was approximately $3.1 million, or less than 8 percent of the funds available for the support of National Eye Institute extramural research projects.

The NEI is now reevaluating the use of center grants and preparing new administrative guidelines for both programs. The purpose is not necessarily to expand their scope but rather to employ them optimally in achieving the mission of the Institute while assuring that the mainstay support for vision research, the individual research project grant, is not jeopardized.

Core Grants for Vision Research Centers

The core grant awarded by the NEI does not provide direct funding for research projects. Rather, it provides a central nucleus or core of resources, facilities, and services which are shared by investigators working on a number of ongoing research projects. Thus, an NEI core grant supports an organization at which there are four or more high-quality, independently-supported research projects in the visual sciences. The core research center grant facilitates multidiscipline research approaches to problems in the visual sciences. The center supports both laboratory and clinical studies and promotes interaction and collaboration among vision researchers and investigators from other departments or areas of interest. The core grant may also provide funds to initiate pilot studies and support the annual salary of one newly-recruited investigator per year. These individuals are expected to use this opportunity to establish their research projects and develop applications for their own research project grants.

Specialized Clinical Research Center Grants

These centers have two outstanding attributes: investigators with the capability to conduct innovative scientific studies in a health care setting and an environment which allows the full promise of these capabilities to come to fruition. Specifically, they feature outstanding clinical expertise and facilities, excellent referral arrangements that assure a steady flow of patients with disorders that require study, a commitment to bring the latest laboratory methods to the clinical research setting, and well-developed insights about the theory and practice of biostatistical and epidemiological techniques.

Animal Models of Human Eye Diseases

In recent years, there has been renewed emphasis in ophthalmic research on the development of animal models. This is because an increasing number of research investigators are attempting to simulate a variety of human eye diseases and techniques are now available for making good use of such valuable resources. Vision scientists rarely have the opportunity to study the total natural history of any human ocular disease and are only able to examine affected tissue, particularly intraocular tissue, when the eye is removed for medical reasons or after death. Lack of sufficient human eyes for histological and biochemical analyses and the need to refine various eye surgical techniques have contributed to the increased requirement for models of human eye disease in nonhuman primates and lower animals.

Research on animal models spans all NEI programs. For example, experimental herpetic keratitis in rabbits has provided a valuable tool for predicting the effectiveness of various antiviral drugs against this corneal disease in man. The extensive study of the mechanism of galactose cataract in rats has led to the definition of the central role of the enzyme aldose reductase in controlling the osmolarity of human lens fiber cells. Experimental visual deprivation of monkeys, cats, and other animals early in life has increased understanding of the development of amblyopia in children. Repeated circumferential argon laser photocoagulation of the trabecular meshwork in rhesus monkeys produces an animal model which mimics human primary open-angle glaucoma. And, rod-cone degeneration observed in taurine-deficient cats and the progressive retinal atrophy that occurs in Norwegian elkhounds are examples of specific ocular models which can be examined histochemically for biochemical clues to the degenerative processes which can occur in the human retina and pigment epithelium.

The successful use of animal models in some NEI-supported projects highlights their unavailability in the majority of human ophthalmic diseases. For instance, a rabbit model for defining predisposing factors in the recurrence of ocular herpes simplex in man is urgently needed. Suitable research animals are also required for investigating the etiology and natural history of adenoviral keratoconjunctivitis as well as herpes zoster infection of the human eye. The most prevalent debilitating form of human cataract is the senile type; yet, at the present time, no animal model has been described which parallels the human condition.

Although neovascular glaucoma is often a serious complication of diabetic retinopathy, the leading cause of new adult blindness in the United States, little progress has been made in understanding the fundamental mechanisms involved in this form of glaucoma because of the lack of an appropriate species of animal for research purposes. New animal analogs of such human disorders as vascular and circulatory abnormalities of the retina, demyelinating diseases of the optic nerve, and prenatal viral infections of the visual system are also needed to provide necessary basic information about energy transduction and information processing in this part of the nervous system.

The NEI supports research into the genetic, morphological, physiological, biochemical, and behavioral aspects of animal models of human eye disease principally through the regular research project grant. Research contracts are considered in those instances where the research animal is well-characterized, but support is needed for maintaining special colonies and distributing animals nationwide to qualified investigators.

Scientific Disciplines of Importance to All Vision Research

The Panel reports summarized in Chapter 5 demonstrate that studies in a full spectrum of basic and applied scientific disciplines are essential for the advancement of vision science. Although vision research is directed to the preservation and restoration of vision and, therefore, classified on the basis of tissue affected and disease process involved, it is important to identify the basic clinical fields of science that contribute to progress in all areas of vision disease. The expansion of knowledge in established biomedical fields and in specialities that have developed more recently is requisite to a thorough understanding of the development, structure, function, and degeneration of the visual system. Equally important is the need for understanding specific disease processes, such as inflammation, neoplasm, and injury, that may be superimposed on this life cycle. This understanding forms the scientific basis for the development of new methods to prevent, diagnose, and treat visual system abnormalities.

Several basic and clinical disciplines of importance to all areas of vision research are noted below, each of which provides distinctive scientific concepts and methodologies. Representative examples of actual or potential contributions of these disciplines to vision science are discussed.

Anatomy, Embryology, and Genetics

Application of the techniques of anatomy, embryology, and genetics to the study of visual system structure and development is worthy of significant attention. A better characterization of the normal structure and abnormal stages in the morphogenesis of key visual system components would enhance understanding and almost inevitably contribute to the prevention, diagnosis, and treatment of major eye diseases. New staining and reconstruction techniques for determining cell structure and ultrastructure are examples of potentially valuable anatomical research. These warrant systematic application in studies of the visual system at all stages of the life cycle. Techniques for culturing human and animal tissue in vitro are well developed as a result of research in other biomedical areas and are readily applicable to investigations of the visual system. Methods for observing and measuring microcirculation are also widely used in other fields and are appropriate for use on the visual system. And, techniques such as radioautography and diffusion tracer studies have important interfaces with other scientific disciplines.

The following are some of the many areas where more knowledge of embryology and development are needed:

- Differentiation and general development of visual system structures;
- Development of the trabecular meshwork and its relationship to glaucoma;
- Development of the sensory retina and its synaptic connections;
- Formation and functional maturation of the retinal pigment epithelium;
- Establishment of the ocular system microcirculation;
- Development of the central nervous system components of vision with particular emphasis on the abnormalities associated with amblyopia;
- Regulation of regeneration in the fetal or neonatal visual system, following surgical intervention, toxic damage, or infection.

The multidiscipline area of genetics is closely associated with the developmental biology of the visual system and the physiological and biochemical events occurring at the various stages of its development. An increasing number of visual system disorders have been shown to be traceable directly or indirectly to inborn errors of metabolism. For example, one form of cataract is related to errors of galactose metabolism.

Clearly, the concepts of genetics should be applied to problems related to vision. Animal models or homologues of human visual abnormalities of genetic origin should be identified, characterized, and where appropriate, made readily available to vision researchers.

There is also the need for more detailed investigation of the natural history of those degenerative phenomena to which the visual system is subject, including the effects of aging. Many important disorders of vision, such as degenerative (senile) cataract, open-angle glaucoma, and macular degeneration, are related to aging processes that are poorly understood. Changes in visual perceptual capabilities with aging have not been systematically assessed. Moreover, other disorders currently classified as degenerative may in fact be the result of toxic factors, metabolic errors, or immunologic insults that require specialized investigation.

Biochemistry and Physiology

The methods of modern physiology and biochemistry have a significant role in new investigations of visual system function in health and disease. These include studies whose goals include a deeper understanding of intracellular metabolism and specific intercellular metabolic relationships; for example, the manner in which the pigment epithelium influences movement of fluids, electrolytes, nutrients, and other materials between the choroid and retina. Also, characterization of mechanisms involved in aqueous humor formation and the regulation of intraocular pressure would have obvious import for the study of glaucoma. In the visual nervous system, changes in the enzymatic regulation of the synthesis, release, breakdown, and reuptake of neurotransmitters may be involved in disorders of perception or eye movement control. Developments in electrophysiological methodology, including new techniques of recording electrical activity in single cells through microelectrode arrays, or electric and magnetic fields associated with brain activity through larger electrodes, may have immediate application in basic vision research or in neurophthalmological diagnosis. Close monitoring of advances in the general field of neurophysiology should be continued because of their potential contribution to visual science, for example, progress in neuroprostheses, or to the treatment of ocular disorders.

Microbiology and Immunology

The disciplines of microbiology and immunology offer substantial research opportunities because the eye is particularly subject to infectious disease and immunologic insult. Improving present means of prevention and treatment will require more knowledge about such topics as the life cycle of pathogenic bacteria and viruses, the factors and events that determine whether a cell becomes infected, and the relationship of drugs to normal and abnormal immunological mechanisms. Immune reaction leading to corneal graft rejection needs further exploration. Cell surface antigens, cell-mediated immunity, and circulating antibodies warrant active investigation. The recent rapid growth in general

knowledge of the immune system and the continued maturation of methodologies for studying immune system processes augur well for successful interaction of this discipline with a number of facets of vision science.

Physical Optics, Physiological Optics, and Psychophysics

The sciences of physical and physiological optics form the foundation of the theory of vision. Traditional research on image formation by the anterior structures of the eye is now being extended by new technology such as lasers for presenting precisely controlled images in optical experiments. Intraocular lens implants are being tested for safety and durability. Prolonged optical correction by fitting a series of specially shaped contact lenses (orthokeratology) is being evaluated.

Advances in electro-optical technology are increasing the precision of eye movement recording and decreasing the obtrusiveness of the devices used. For example, new infrared light sensor systems permit eye-tracking using reflections from the cornea and lens, without the attachment of any recording devices to the subject. Such new techniques promise to improve diagnosis of disorders of oculomotor control, for example, congenital nystagmus and ophthalmoplegia.

Psychophysics, the science that relates physical stimulation to perceived sensation and perception, has a long history of ophthalmic usefulness for testing visual sensitivity, acuity, and color perception. Today, traditional methods in visual psychophysics are being complemented by new techniques such as the spatial frequency analysis of stimulus patterns, contrast modulation sensitivity functions, and measurements of facilitory and inhibitory interactions among neighboring receptor cells in the retina. These quantitative approaches to vision testing promise to provide the clinician with new noninvasive diagnostic instruments to identify and localize retinal or central nervous system pathology. The psychophysical evaluation of acquired, as well as hereditary, color vision defects also has great ophthalmic potential. Research on rehabilitation technology for severely visually handicapped and blind patients, particularly vision substitution systems, also deserves continued support.

Systems Theory and Computer Science

Mathematical modeling of the visual system can be expected to increase in importance as vision science progresses. A noteworthy development in this respect is the use of neurological control systems analysis in exploring the regulation of eye movements in health and disease. Systems theory supplies a synthesis of what is known about oculomotor mechanisms, generates specific hypotheses for further experimental testing, and creates a basis for a quantitative diagnosis of neurophthalmic disease. Computer assistance for the solution of complex equations, or for the simulation of response to various stimuli, is often required in this field. Developments in computer science should be monitored in order to ascertain their possible application to vision research. Increasing dependence on computers for generating and presenting stimuli in both the laboratory and the clinic is inevitable.

Pharmacology

Another major focus of vision research is the discipline of pharmacology. Aside from research related to the traditional role of drugs in the therapy of such eye

diseases as glaucoma and herpes simplex keratitis, investigations of pharmacological agents are becoming increasingly important in basic research on the visual system. Neurotransmitters in the retina and excitatory or inhibitory synaptic chemical mediators in the visual central nervous system are examples of subjects which warrant substantial research. And, drugs that selectively perturb the physiological and biochemical mechanisms in laboratory animals are becoming increasingly valuable as means for providing new knowledge. Two illustrations of the latter are the experimental induction of cataracts with galactose and the alteration of vascular permeability within the eye with prostaglandins. The interactions between exogenous chemical subtances and the visual process offer a rich array of investigative challenges to scientists who may draw upon the mainstream of pharmacological concepts and methodology.

Pathology

Pathology, the scientific discipline concerned with disease processes and the course of disease, is traditionally important at the interface of basic science investigation and clinical disease. Increased use of the full range of histopathological techniques in the study of induced and naturally occurring disease in animals is warranted. For example, the use of histopathology to characterize the course of animal diseases resembling retinitis pigmentosa is certain to offer insight into normal retinal structure and the aberrations that may result from disruption of normal processes. With human tissue obtained at surgery and at autopsy, comparable utilization of histopathologic methodology is very likely to provide valuable information about disease processes such as corneal dystrophy, cataract, glaucoma, and retinal storage diseases.

Epidemiology

The application to vision research of both epidemiology and the discipline of biomathematics is also likely to provide extremely useful information. Because most vision disorders do not lead directly to death but, rather, impose chronic functional deficits on the victims, it is especially critical to describe and quantify the social impact of these diseases in both human and economic terms. Thorough studies of the incidence and clinical course of these disorders in large populations and under a variety of circumstances are a key to pinpointing the most important problems for vision research, to uncovering clues concerning etiology and pathogenesis, and to assessing the use of improved methods for prevention, diagnosis, and treatment.

The National Eye Institute and Knowledge Transfer*

In testimony before the Senate Subcommittee on Health in 1976, Donald S. Fredrickson, M.D., Director of the National Institutes of Health, said:

> *It seems clear that in the future, the NIH and the rest of the scientific community must assume more responsibility for the effect of research on the quality of health*

* Parts of this discussion are extracted from draft NIH position papers.

care delivered. The need for accelerating the transfer of new technology across the 'interface' between biomedical research and the health care community and systems is a major issue.

* * *

*[One] responsibility is to understand more fully and to improve the somewhat informal system whereby consensus is reached concerning the validity of the interventions arising from our research.***

How to assure the effective and appropriate application of new knowledge gained through research to practical uses in health care is a longstanding problem in all areas of medicine, including eye care. Interest in this subject has intensified in recent years because of increasing public demand for better health care and the greater complexity and cost of new health technologies. From time to time, the government has tried to intervene in this area, with variable results. Several attempts have been made to complement the successful efforts of NIH in fostering categorical biomedical research with programs of demonstration and disease control, health education, and health screening. On several occasions, NIH itself was assigned responsibility for health programs that fell outside of its traditional research mission. Disease control programs, for example, were an integral part of the National Cancer Institute in the late 1930's and are so today. The Regional Medical Programs in the late 1960's, which were designed to broaden public access to the latest health care advances—particularly in heart disease, cancer, and stroke—started out under NIH administration.

In time, most of the nonbiomedical research functions of NIH were transferred to other government health agencies, but subsequently, most of these were eliminated. Now, once again, because of growing concerns over the quality and cost of health care, NIH is being asked by the Congress and others to undertake programs which will facilitate the appropriate application of biomedical research results. This would include expansion of present evaluative research activities, typified by clinical trials, which have only recently been accepted as a legitimate activity of the federal government.

Defining the nature and extent of NIH's involvement in such efforts—given the record of federal interventions in this area and the known pitfalls—has understandably been the subject of much debate. At stake is the very future of NIH; it somehow must assume a larger role in the Nation's health care system without having its credibility and effectiveness as a research agency dissipated by entanglements in issues and activities beyond its power to influence or control. Yet, there is no question of the increasing need for effective action in this area. It is evident that NIH with its organization of categorical Institutes, their associated National Advisory Councils, and the network of collaborating investigators and institutions within the research community should be the logical focus of leadership in addressing these problems.

Health Spectrum

To place in perspective the current quandary over defining the proper limits of the NIH role in knowledge transfer, it is useful to outline the spectrum of health

** "Basic Issues in Biomedical and Behavioral Research, 1976." Hearings Before the Subcommittee on Health of the Committee on Labor and Public Welfare, United States Senate, Ninety-Fourth Congress, Second Session, on Examination of Public Policy in the Area of Biomedical and Behavioral Research, June 16 and 17, 1976, United States Government Printing Office, Washington, DC, 1976, pp 111-112.

activities in which NIH either now participates or may play some role in the future. These activities can be viewed as a continuum ranging from fundamental research to prevention and patient care programs:

- Biomedical Research
  - Identifying gaps in knowledge applicable to health and disease problems;
  - Developing through research an information base in response to this need;
  - Interrelating new knowledge with previously existing knowledge;
  - Applying research findings to clinical problems.
  - Validating research results. (This encompasses questions of safety, usefulness, and superiority to interventions already available.)
- Technical Consensus—Agreement among all parties concerned that a new intervention in the delivery of health care is scientifically sound and technically feasible. This includes scientific/medical agreement on:
  - The clinical significance of new findings;
  - Whether a given innovation has been proven safe and efficacious and if not, what more needs to be done to obtain such evidence.
- Health Services Research
  - Assessing the feasibility of introducing new laboratory or clinical research results into the health care system;
  - Determining the cost/effectiveness of new scientifically validated health care procedures.
- Interface Consensus—The information and recommendations emerging from biomedical research, technical consensus, and health services research are considered by all relevant parties including professional societies, voluntary health agencies, regulatory agencies, fiduciaries, service agencies, and consumers. These groups must agree that a given intervention is suitable for introduction into practice. They must consider:
  - Whether cost, ethical, or other social impacts have been adequately examined;
  - Whether recommendations are phrased for ready understanding and acceptance by health practitioners and include all appropriate cautions;
  - Whether there is need for community demonstration or feasibility studies before widespread application can take place.
- Dissemination and Application
  - Diffusion of recommendations about preventive, diagnostic, therapeutic, and rehabilitative health care procedures, along with the supporting knowledge and a description of the consensus-building processes which produced them;
  - Acceptance and application by the practitioner community and the public.

Problems in Knowledge Transfer

Concern that new knowledge is not being systematically and effectively transferred from research to health care has been accompanied recently by

concern that new research knowledge may in some instances actually contribute to increasing the already enormous costs of health care. Critics have pointed, for example, to the high cost of such so-called "half-way technologies" as renal dialysis and some of the complex and costly therapies for cancer. Although many of the cost-impact criticisms of research are arguable, such concerns must be taken seriously.

In identifying options for NIH to deal with the general problem of research knowledge transfer, the strengths and weaknesses of the processes by which the research community presently transmits its findings to the health care delivery system and to the public must be taken into account.

Lessons can also be learned from the experiences of past and present federal programs which relate to health care delivery. For, although many government programs are aimed at addressing problems in the organization, funding, and delivery of health services, these topics remain a subject of continuing scrutiny and debate. At the Senate hearings mentioned earlier, for instance, members of the Subcommittee on Health questioned the effectiveness of current methods for disseminating information to practitioners and the public concerning scientific discoveries ready for general application. It was suggested that deficiencies in this information flow are partly responsible for the uneven quality of health and medical care across the Nation. It has been suggested further that the research community and the NIH have a responsibility to help assure that the best medical interventions are widely and appropriately utilized. The President's Biomedical Research Panel concluded that the problem was not one of inordinate delay between the development of an intervention and its general availability, but rather that there were "frequent and substantial time lags between the first clinical application of a discovery and [its] widespread use by practicing physicians and, indeed, acceptance by patients."* But, the Panel also expressed its concern that laboratory developments may in some instances actually be applied to health care too quickly without adequate evaluation or development of consensus on its proper application. "Such premature acceptance can pose just as serious a threat to the Nation's health as any . . . delay in making new and proven technologies available," the Panel noted.

Fostering the clinical testing, dissemination, and effective utilization of information pertinent to health care delivery and patient management could be considered the potential responsibility of at least a dozen federal agencies. These programs are already very large and encompass health care delivery, regulation, and research. Yet, the roles and responsibilities of these agencies are not sufficiently well integrated to eliminate the deficiencies under discussion here, and gaps in coverage abound.

The present system for transfer of knowledge between research programs and health service delivery thus has more than one defect: a piecemeal apparatus for upgrading professional and public awareness of the changing content of health care, a lack of formal, systematic programs both within the government and between the federal agencies and the health care community for transfer of new technologies, and a paucity of structured and orderly mechanisms for reaching consensus on the validity, effectiveness, and usefulness of the many products of biomedical and health services research.

* Report of the President's Biomedical Research Panel, US DHEW Publ No (OS) 76-500, Washington, DC, April 30, 1976, pp 9-10.

Potential National Eye Institute Responsibilities

With these deficiencies in mind, the key questions for the National Eye Institute relate to the extent to which it should assume responsibility for:

- Validation of new and traditional medical and surgical methods for prevention, diagnosis, treatment, and rehabilitation related to eye and vision care.
- Improvement of the informal system whereby consensus is reached concerning the validity and significance of new findings arising from vision research and their readiness for wide clinical application.
- Assessment of the nonmedical implications (e.g. social, ethical, economic) of new findings.
- Evaluation of cost containment strategies, where research advances may appear to lead to treatments which are more costly, albeit more efficacious, than those previously available.
- Dissemination of research results, beyond traditional channels of scientific communication.

Recommended National Eye Institute Role

As the field of vision research continues to expand and become increasingly productive, the National Advisory Eye Council believes that the National Eye Institute and the rest of the vision research community must assume greater responsibility for assuring that the knowledge gained from research is, at a suitable time and in appropriate manner, incorporated into the delivery of eye care.

In particular, the National Eye Institute—with guidance from the National Advisory Eye Council—should establish a formal procedure for identifying new vision research knowledge which is ready for application to disease prevention, detection, diagnosis, treatment, or rehabilitation and act to ensure that this data is appropriately processed for effective transfer to the eye and vision care community. Essentially, this will involve monitoring progress in selected areas of vision research, recognizing the time when a particular development or intervention has progressed sufficiently that it is timely to undertake clinical trials and other studies of its validity, usefulness, and appropriateness; deciding whether and how a reasonable technical consensus concerning its application can be achieved; and collaborating as appropriate with other federal agencies which have responsibility for cost/benefit analyses and other forms of health services research, regulatory actions, establishment of ethical standards, and payment for health services. This responsibility, on occasion, will require identification of interventions which are not yet ready for introduction into the health care system, but whose potential contribution is so great that extraordinary steps are justified to assure their rapid further development to a point where definitive evaluation can be undertaken.

It is important to emphasize that this new activity—the assessment and transfer of new knowledge—must be provided with its own resources, including funds, manpower, and space, and must not be undertaken at the expense of the NEI's successful program of research support. Indeed, without the continued growth and development of basic and applied research, there will be no new knowledge to be assessed or transferred. The expansion of the NEI mission into knowledge transfer activities should therefore be undertaken cautiously in the

context of an integrated plan for the accomplishment of the Institute's goals and objectives.

At this time, it seems reasonable, therefore, that the National Eye Institute's role should be limited primarily to fostering the validation of new and established medical and surgical interventions, facilitating consensus development, and encouraging the coordinated dissemination of research results. The economic and social considerations of health care delivery are beyond the present expertise of the National Eye Institute. In any event, it is important that the NEI's role in knowledge transfer evolve carefully over time with the advice and guidance of the Council and other organizations interested in eye care and vision research.

8

Program Planning Participants

National Advisory Eye Council

MRS. FRANK PEARCE ATKINS (1979)*
Cincinnati, Ohio

TONY Q. CHAN, O.D. (1979)
5341 Wyoming Boulevard, Northeast
Albuquerque, New Mexico

JERRY LEE CHRISTENSEN, PH.D. (1980)
Associate Professor and Chairman
Department of Physiological Optics
School of Optometry
University of Alabama
Birmingham, Alabama

FLORENCE DUNBAR, PH.D.**
Attorney at Law
Chicago, Illinois

JAY M. ENOCH, PH.D.**
Graduate Research Professor
Department of Ophthalmology
College of Medicine
University of Florida
Gainesville, Florida

W. MORTON GRANT, M.D. (1977)
David Glendenning Cogan Professor
of Ophthalmology
Harvard Medical School
Boston, Massachusetts

JOHN E. HARRIS, M.D. (1978)
Professor and Chairman
Department of Ophthalmology
Medical School
University of Minnesota
Minneapolis, Minnesota

GORDON G. HEATH, O.D., PH.D. (1980)
Dean
School of Optometry
Indiana University
Bloomington, Indiana

A. EDWARD MAUMENEE, M.D. (1978)
Director
Wilmer Ophthalmological Institute
School of Medicine
Johns Hopkins University
Baltimore, Maryland

G. RICHARD O'CONNOR, M.D. (1977)
Director
Francis I. Proctor Foundation
for Research in Ophthalmology
University of California,
San Francisco
San Francisco, California

LORRIN A. RIGGS, PH.D. (1980)
Professor Emeritus of Psychology
Brown University
Providence, Rhode Island

CHARLES L. SCHEPENS, M.D. (1977)
President
Eye Research Institute of
Retina Foundation
Boston, Massachusetts

HARRY G. SPERLING, PH.D. (1979)
Professor and Director
Sensory Sciences Center
Graduate School of Biomedical Science
University of Texas Health
Science Center
Houston, Texas

* Four year term expires.
** Term completed 1976.

BRADLEY R. STRAATSMA, M.D.**
Director
Jules Stein Eye Institute and
Professor and Chairman
Department of Ophthalmology
School of Medicine
University of California,
Los Angeles
Los Angeles, California

TOMMIE M.A. YOUNG, PH.D. (1978)
Professor and Director
F.D. Bluford Library
North Carolina Agricultural and
Technical State University
Greensboro, North Carolina

NOBLE J. DAVID, M.D.
(ex officio)
Chief
Neurology Service
Veterans Administration Hospital and
Professor of Neurology and
Associate Professor of Ophthalmology
University of Miami
Miami, Florida

COLONEL RAYMOND J. PETRAUSKAS, M.D.
(ex officio)
Chief
Department of Ophthalmology
Andrews Air Force Base
Washington, D.C.

National Advisory Eye Council Program Planning Subcommittee

Chairman

A. EDWARD MAUMENEE, M.D.
Director
Wilmer Ophthalmological Institute
School of Medicine
Johns Hopkins University
Baltimore, Maryland

Members

JOHN LOTT BROWN, PH.D.
Director
Center for Visual Sciences
University of Rochester
Rochester, New York

V. EVERETT KINSEY, PH.D.
Director Emeritus
Institute of Biological Sciences
Oakland University
Rochester, Michigan

G. RICHARD O'CONNOR, M.D.
Director
Francis I. Proctor Foundation
for Research in Ophthalmology
University of California
San Francisco
San Francisco, California

CHARLES L. SCHEPENS, M.D.
President
Eye Research Institute of
Retina Foundation
Boston, Massachusetts

BRADLEY R. STRAATSMA, M.D.
Director
Jules Stein Eye Institute and
Professor and Chairman
Department of Ophthalmology
School of Medicine
University of California,
Los Angeles
Los Angeles, California

Panel Members and Consultants

Retinal and Choroidal Diseases

Chairman

ALAN M. LATIES, M.D.
Irene Heinz Given and
John Laporte Given
Professor of Ophthalmology and
Director of Research
Scheie Eye Institute
School of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

Members

DANIEL M. ALBERT, M.D.
Professor of Ophthalmology
Harvard Medical School
Boston, Massachusetts

MARY BETH BURNSIDE, PH.D.
Associate Professor of Anatomy
University of California, Berkeley
Berkeley, California

RONALD E. CARR, M.D.
Professor of Ophthalmology
School of Medicine
New York University
New York, New York

HAROLD E. CROSS, M.D., PH.D.
Professor and Head
Section of Ophthalmology
College of Medicine
University of Arizona
Tucson, Arizona

JOHN E. DOWLING, PH.D.
Professor of Biology
Harvard University
Cambridge, Massachusetts

DANIEL FINKELSTEIN, M.D.
Assistant Professor of Ophthalmology
Wilmer Ophthalmological Institute
School of Medicine
Johns Hopkins University
Baltimore, Maryland

MATTHEW M. LA VAIL, PH.D.
Associate Professor of Anatomy
School of Medicine
University of California,
San Francisco
San Francisco, California

WERNER K. NOELL, M.D.
Professor of Physiology and
Head
Division of Neural Biology
School of Medicine
State University of New York
at Buffalo
Buffalo, New York

G. RICHARD O'CONNOR, M.D.
(ex officio)
Director
Francis I. Proctor Foundation
for Research in Ophthalmology
University of California,
San Francisco
San Francisco, California

CHARLES L. SCHEPENS, M.D.
(ex officio)
President
Eye Research Institute of
Retina Foundation
Boston, Massachusetts

Consultants

GUSTAVO AGUIRRE, D.V.M.
Assistant Professor of Ophthalmology
Department of Clinical Studies
School of Veterinary Medicine
University of Pennslyvania
Philadelphia, Pennsylvania

ADELBERT AMES, M.D.
Professor of Physiology
Harvard Medical School
Boston, Massachusetts

LOYAL E. APPLE
Executive Director
American Foundation
for the Blind, Inc.
New York, New York

ENDRE A. BALAZS, M.D.
Malcom P. Aldrich Professor
of Ophthalmology and
Director of Research
College of Physicians and Surgeons
Columbia University
New York, New York

HOWARD BERNSTEIN, M.D.
10401 Old Georgetown Road
Bethesda, Maryland

C. DAVID BRIDGES, PH.D.
Professor of Ophthalmology
Baylor College of Medicine
Houston, Texas

ROBERT P. BURNS, M.D.
Professor of Ophthalmology
Health Sciences Center
University of Oregon
Portland, Oregon

JOHN H. CARTER, O.D., PH.D.
Acting Director
Primary Care Division and
Academic Dean
New England College of Optometry
Boston, Massachusetts

ALFRED COULOMBRE, PH.D.
Chief
Section on Experimental
Embryology
Laboratory of Vision Research
National Eye Institute
Bethesda, Maryland

WILLIAM W. DAWSON, PH.D.
Professor of Ophthalmology
and Physiology
College of Medicine
University of Florida
Gainesville, Florida

FRANCOIS DELORI, PH.D.
Associate Scientist
Eye Research Institute of
Retina Foundation
Boston, Massachusetts

JAY M. ENOCH, PH.D.
Graduate Research Professor
Department of Ophthalmology
College of Medicine
University of Florida
Gainesville, Florida

ROBERT N. FRANK, M.D.
Professor of Ophthalmology
School of Medicine
Wayne State University
Detroit, Michigan

FREDERICK T. FRAUNFELDER, M.D.
Professor and Chairman
Department of Ophthalmology
University of Arkansas
for Medical Sciences
Little Rock, Arkansas

SIDNEY FUTTERMAN, PH.D.
Professor of Ophthalmology
School of Medicine
University of Washington
Seattle, Washington

MORTON F. GOLDBERG, M.D.
Chairman
Department of Ophthalmology
Abraham Lincoln School of Medicine
University of Illinois
Chicago, Illinois

EVANGELOS GRAGOUDAS, M.D.
Instructor in Ophthalmology
Harvard Medical School
Boston, Massachusetts

DANIEL G. GREEN, PH.D.
Professor of Ophthalmology
Medical School
University of Michigan
Ann Arbor, Michigan

ELLIS GRUBER, M.D.
Rochester Ophthalmological Group
1675 Monroe Avenue
Rochester, New York

PAUL HENKIND, M.D., PH.D.
Professor and Chairman
Department of Ophthalmology
Montefiore Hospital and
Medical Center
New York, New York

JOE G. HOLLYFIELD, PH.D.
Associate Professor of Ophthalmology
Baylor College of Medicine
Houston, Texas

RICHARD HOOVER, M.D.
Assistant Professor of Ophthalmology
Wilmer Ophthalmological Institute
School of Medicine
Johns Hopkins University
Baltimore, Maryland

ERWIN HULTSCH, M.D
Assistant Scientist
Department of Retina Research
Eye Research Institute of
Retina Foundation
Boston, Massachusetts

JULE G. JOSE, O.D., PH.D.
Assistant Professor of Optometry
and Physiological Optics
University of California, Berkeley
Berkeley, California

PAUL KAUFMAN, M.D.
Assistant Professor of Ophthalmology
Medical School
University of Wisconsin
Madison, Wisconsin

THEODORE LAWWILL, M.D.
Associate Professor of Ophthalmology
School of Medicine
University of Louisville
Louisville, Kentucky

PAUL LIEBMAN, M.D.
Professor of Anatomy
School of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

MICHAEL F. MARMOR, M.D.
Assistant Professor of Surgery
School of Medicine
Stanford University
Stanford, California

IRENE H. MAUMENEE, M.D.
Assistant Professor of Ophthalmology
and of Medicine
Wilmer Ophthalmological Institute
School of Medicine
Johns Hopkins University
Baltimore, Maryland

RONALD MICHELS, M.D.
Assistant Professor of Ophthalmology
Wilmer Ophthalmological Institute
School of Medicine
Johns Hopkins University
Baltimore, Maryland

JOHN W. PATTERSON, M.D., PH.D.
Professor of Physiology
School of Medicine
University of Connecticut
Farmington, Connecticut

ARNALL PATZ, M.D.
Professor of Ophthalmology
Wilmer Ophthalmological Institute
School of Medicine
Johns Hopkins University
Baltimore, Maryland

BENIGNO PECZON, PH.D.
Assistant Scientist
Eye Research Institute of
Retina Foundation
Boston, Massachusetts

GHOLAM PEYMAN, M.D.
Professor of Ophthalmology
Illinois Eye and Ear Infirmary
University of Illinois
Chicago, Illinois

DONALD G. PITTS, O.D., PH.D.
Professor of Physiological Optics
and Optometry
College of Optometry
University of Houston
Houston, Texas

OLEG POMERANTZEFF, D.ENG
Senior Scientist
Eye Research Institute of
Retina Foundation
Boston, Massachusetts

SAUL PRESBERG, M.D.
Rochester Ophthalmological Group
1675 Monroe Avenue
Rochester, New York

ELIO RAVIOLA, M.D.
Professor of Anatomy
Harvard Medical School
Boston, Massachusetts

LIANE REIF-LEHRER, PH.D.
Senior Scientist
Eye Research Institute of
Retina Foundation
Boston, Massachusetts

LT. COLONEL ROY H. RENGSTORFF, O.D., PH.D.
United States Army
Biomedical Laboratory
Edgewood
Aberdeen Proving Ground, Maryland

HARRIS RIPPS, PH.D.
Professor of Ophthalmology
School of Medicine
New York University
New York, New York

CHARLES RIVA, SC.D.
Associate Scientist
Department of Retina Research
Eye Research Institute of
Retina Foundation
Boston, Massachusetts

RICHARD M. ROBB, M.D.
Ophthalmologist-in-Chief
Children's Hospital Medical Center
Boston, Massachusetts

STEPHEN J. RYAN, M.D.
Professor and Chairman
Department of Ophthalmology
School of Medicine
University of Southern California
Los Angeles, California

SUSAN Y. SCHMIDT, PH.D.
Assistant Professor of Ophthalmology
Harvard Medical School
Boston, Massachusetts

S. MURRAY SHERMAN, PH.D.
Associate Professor of Physiology
School of Medicine
University of Virginia
Charlottesville, Virginia

ARTHUR M. SILVERSTEIN, PH.D.
Professor of Ophthalmology
Wilmer Ophthalmological Institute
School of Medicine
Johns Hopkins University
Baltimore, Maryland

ROY H. STEINBERG, M.D., PH.D.
Professor of Physiology
and Ophthalmology
School of Medicine
University of California,
San Francisco
San Francisco, California

INGOLF H. WALLOW, M.D.
Associate Professor of Ophthalmology
Medical School
University of Wisconsin
Madison, Wisconsin

JOSE A. ZADUNAISKY, M.D.
Professor of Ophthalmology
School of Medicine
New York University
New York, New York

Corneal Diseases

Chairman

HERBERT E. KAUFMAN, M.D.
Professor and Chairman
Department of Ophthalmology
School of Medicine
University of Florida
Gainesville, Florida

Members

STUART I. BROWN, M.D.
Professor and Chairman
Department of Ophthalmology
Eye and Ear Hospital
University Health Center
of Pittsburgh
Pittsburgh, Pennsylvania

CLAES-HENRIK DOHLMAN, M.D.
Director and Senior Scientist
Department of Cornea Research
Eye Research Institute of
Retina Foundation
Boston, Massachusetts, and
Professor and Chairman
Department of Ophthalmology
Massachusetts Eye and Ear Infirmary
Harvard Medical School
Boston, Massachusetts

DAN B. JONES, M.D.
Associate Professor of Ophthalmology
Baylor College of Medicine
Houston, Texas

ROBERT MANDELL, O.D., PH.D.
Professor of Optometry and
Physiological Optics and
Associate Dean
School of Optometry
University of California, Berkeley
Berkeley, California

DAVID M. MAURICE, PH.D.
Adjunct Professor of Surgery
School of Medicine
Stanford University
Stanford, California

A. EDWARD MAUMENEE, M.D.
(ex officio)
Director
Wilmer Ophthalmological Institute
School of Medicine
Johns Hopkins University
Baltimore, Maryland

Consultants

MICHAEL BERMAN, M.D.
Associate Scientist
Department of Cornea Research
Eye Research Institute of
Retina Foundation
Boston, Massachusetts

CHARLES K. BEYER, M.D.
Assistant Clinical Professor
of Ophthalmology
Harvard Medical School
Boston, Massachusetts

PERRY S. BINDER, M.D.
Chief
Section of Ophthalmology
Veterans Administration Hospital and
Associate Professor of
Surgery/Ophthalmology
University of California,
San Diego
La Jolla, California

W. BENTON BOONE, M.D.
Assistant Professor of Ophthalmology
College of Medicine
University of California,
Irvine
Irvine, California

WILLIAM M. BOURNE, M.D.
Assistant Professor of Ophthalmology
Mayo Medical School
Rochester, Michigan

ROBERT P. BURNS, M.D.
Professor of Ophthalmology
Health Sciences Center
University of Oregon
Portland, Oregon

H. DWIGHT CAVANAUGH, M.D.
Associate Professor of Ophthalmology
School of Medicine
Emory University
Atlanta, Georgia

JOHN W. CHANDLER, JR., M.D.
Associate Professor of Ophthalmology
School of Medicine
University of Washington
Seattle, Washington

ROBERT L. CHURCH, M.D.
Associate Professor of Ophthalmology
and Anatomy and Cell Biology
Eye and Ear Hospital
University Health Center
of Pittsburgh
Pittsburgh, Pennsylvania

CHARLES CINTRON, PH.D.
Associate Scientist
Department of Cornea Research
Eye Research Institute of
Retina Foundation
Boston, Massachusetts

EDWARD M. COTLIER, M.D.
Professor
Department of Ophthalmology
and Visual Sciences
School of Medicine
Yale University
New Haven, Connecticut

ALFRED J. COULOMBRE, PH.D.
Chief
Section on Experimental
Embryology
Laboratory of Vision Research
National Eye Institute
Bethesda, Maryland

CHANDLER R. DAWSON, M.D.
Professor in Residence and
Associate Director
Francis I. Proctor Foundation
for Research in Ophthalmology
University of California,
San Francisco
San Francisco, California

DONALD J. DOUGHMAN, M.D.
Associate Professor of Ophthalmology
Medical School
University of Minnesota
Minneapolis, Minnesota

HENRY F. EDELHAUSER, PH.D.
Professor of Physiology and
Ophthalmology
School of Medicine
Medical College of Wisconsin
Milwaukee, Wisconsin

JAMES H. ELLIOTT, M.D.
Professor and Chairman
Department of Ophthalmology
School of Medicine
Vanderbilt University
Nashville, Tennessee

JAY M. ENOCH, PH.D.
Graduate Research Professor
Department of Ophthalmology
College of Medicine
University of Florida
Gainesville, Florida

IAN FREEMAN, M.D.
Assistant Professor of Ophthalmology
Eye and Ear Hospital
University Health Center
of Pittsburgh
Pittsburgh, Pennsylvania

ANTONIO R. GASSETT, M.D.
Associate Professor of Ophthalmology
College of Medicine
University of Florida
Gainesville, Florida

ILENE K. GIPSON, PH.D.
Assistant Professor of Ophthalmology
Health Sciences Center
University of Oregon
Portland, Oregon

WILLIAM R. GREEN, M.D.
Professor of Ophthalmology and
Associate Professor of Pathology
Wilmer Ophthalmological Institute
School of Medicine
Johns Hopkins University
Baltimore, Maryland

ARTHUR S. GROVE, JR., M.D.
Assistant Professor of Ophthalmology and
Director
Ophthalmic and Plastic and
Reconstructive Surgery
Massachusetts Eye and Ear Infirmary
Harvard Medical School
Boston, Massachusetts

RICHARD M. HILL, O.D., PH.D.
Professor and Chairman
Department of Physiological Optics
College of Optometry
Ohio State University
Columbus, Ohio

FRANK B. HOEFLE, M.D.
Assistant Professor of Clinical
Ophthalmology
College of Physicians and Surgeons
Columbia University
New York, New York

FRANK J. HOLLY, PH.D.
Associate Scientist
Department of Cornea Research
Eye Research Institute of
Retina Foundation
Boston, Massachusetts

FREDERICK A. JACOBIEC, M.D.
Instructor of Clinical Ophthalmology
College of Physicians and Surgeons
Columbia University
New York, New York

RONALD L. KERNS, O.D.
Associate Professor of Optometry
College of Optometry
Pacific University
Forest Grove, Oregon

GORDON K. KLINTWORTH, M.D., PH.D.
Professor of Pathology
School of Medicine
Duke University
Durham, North Carolina

PETER R. LAIBSON, M.D.
Director of Cornea Service
Wills Eye Hospital
Philadelphia, Pennsylvania

MICHAEL A. LEMP, M.D.
Assistant Professor of Ophthalmology and
Director of Cornea Service
School of Medicine
Georgetown University
Washington, D.C.

IRVING H. LEOPOLD, M.D.
Professor and Chairman
Department of Ophthalmology
College of Medicine
University of California,
Irvine
Irvine, California

GERALD E. LOWTHER, O.D., PH.D.
College of Optometry
Ohio State University
Columbus, Ohio

IRENE H. MAUMENEE, M.D.
Assistant Professor of Ophthalmology
and of Medicine
Wilmer Ophthalmological Institute
School of Medicine
Johns Hopkins University
Baltimore, Maryland

BERNARD McCAREY, PH.D.
Assistant Professor of Ophthalmology
College of Medicine
University of Florida
Gainesville, Florida

ROBERTA L. MEYERS, PH.D.
Associate Professor of Ophthalmology
Jules Stein Eye Institute
School of Medicine
University of California,
Los Angeles
Los Angeles, California

ANTHONY B. NESBURN, M.D.
Head
Cornea and Virology Research Unit and
Associate Professor of Clinical
Ophthalmology
Estelle Doheny Eye Foundation
University of Southern California
Los Angeles, California

DENIS O'DAY, M.D.
Professor of Ophthalmology
School of Medicine
Vanderbilt University
Nashville, Tennessee

DEBORAH PAVAN-LANGSTON, M.D.
Associate Clinical Professor
of Ophthalmology
Massachusetts Eye and Ear Infirmary
Harvard Medical School
Boston, Massachusetts

FRANK M. POLACK, M.D.
Professor of Ophthalmology
College of Medicine
University of Florida
Gainesville, Florida

DINESH O. SHAH, PH.D.
Professor of Anesthesiology
and Chemical Engineering
College of Medicine
University of Florida
Gainesville, Florida

ARTHUR M. SILVERSTEIN, PH.D.
Professor of Ophthalmology
Wilmer Ophthalmological Institute
School of Medicine
Johns Hopkins University
Baltimore, Maryland

WALTER J. STARK, M.D.
Associate Professor of Ophthalmology
Wilmer Ophthalmological Institute
School of Medicine
Johns Hopkins University
Baltimore, Maryland

ORKAN STASIOR, M.D.
Clinical Associate Professor
of Ophthalmology
Albany Medical College
of Union University
Albany, New York

JACK G. STEVENS, D.V.M., PH.D.
Professor of Medical Microbiology
and Immunology
School of Medicine
University of California,
Los Angeles
Los Angeles, California

H. LEE STEWART, M.D.
Assistant Clinical Professor
of Ophthalmology
School of Medicine
University of California,
San Francisco
San Francisco, California

STEPHEN L. TROKEL, M.D.
Assistant Professor of Clinical
Ophthalmology
College of Physicians and Surgeons
Columbia University
New York, New York

STEVEN R. WALTMAN, M.D.
Ophthalmologist
School of Medicine
Washington University
St. Louis, Missouri

CAROLE E. WEST, M.D.
Ophthalmologist
Detroit Institute of Ophthalmology
Detroit, Michigan

FRED M. WILSON, JR., M.D.
Professor and Chairman
Department of Ophthalmology
School of Medicine
Indiana University
Indianapolis, Indiana

Cataract

Chairman

EDWARD M. COTLIER, M.D.
Professor
Department of Ophthalmology
and Visual Sciences
School of Medicine
Yale University
New Haven, Connecticut

Members

GEORGE BENEDEK, PH.D.
Professor of Physics
Massachusetts Institute of
Technology
Cambridge, Massachusetts

LEO T. CHYLACK, JR., M.D.
Assistant Professor of Ophthalmology
Harvard Medical School and
Ophthalmologist-in-Chief
Peter Bent Brigham Hospital
Boston, Massachusetts

ROBERT C. DREWS, M.D.
Ophthalmologist
School of Medicine
Washington University
St. Louis, Missouri

JOHN E. HARRIS, M.D.
Professor and Chairman
Department of Ophthalmology
Medical School
University of Minnesota
Minneapolis, Minnesota

JIN H. KINOSHITA, PH.D.
Chief
Laboratory of Vision Research
National Eye Institute
Bethesda, Maryland

VENKAT N. REDDY, PH.D.
Director
Institute of Biological Sciences
Oakland University
Rochester, Michigan

ALFRED SOMMER, M.D.
Instructor of Ophthalmology
Wilmer Ophthalmological Institute
School of Medicine
Johns Hopkins University
Baltimore, Maryland

ABRAHAM SPECTOR, PH.D.
Professor of Ophthalmological Biochemistry
College of Physicians and Surgeons
Columbia University
New York, New York

JOHAN ZWAAN, M.D.
Instructor of Ophthalmology and
Associate Professor of Anatomy
Albany Medical College
of Union University
Albany, New York

V. EVERETT KINSEY, PH.D.
(ex officio)
Director Emeritus
Institute of Biological Sciences
Oakland University
Rochester, Michigan

Consultants

G. WINSTON BARBER, PH.D.
Chief
Department of Biochemistry
Wills Eye Hospital
Philadelphia, Pennsylvania

NICHOLAS BROWN, F.R.C.S.
Institute of Ophthalmology
University of London
London, England

OSCAR A. CANDIA, M.D.
Associate Professor of Ophthalmology
Mount Sinai School of Medicine
New York, New York

ALPHONSE CINOTTI, M.D.
Professor and Acting Chairman
Department of Ophthalmology
College of Medicine and Dentistry
of New Jersey
Newark, New Jersey

DAVID EIFRIG, M.D.
Professor and Chairman
Department of Ophthalmology
School of Medicine
University of North Carolina
Chapel Hill, North Carolina

JAY M. ENOCH, PH.D.
Graduate Research Professor
Department of Ophthalmology
College of Medicine
University of Florida
Gainesville, Florida

CLIFFORD V. HARDING, PH.D.
Professor of Ophthalmology
School of Medicine
Wayne State University
Detroit, Michigan

JOSEPH HORWITZ, PH.D.
Associate Professor of
Ophthalmology/Biophysics
Jules Stein Eye Institute
School of Medicine
University of California,
Los Angeles
Los Angeles, California

HAROLD L. KERN, SC.D.
Associate Professor of Ophthalmology
Albert Einstein College of Medicine
New York, New York

JOHN F. KUCK, JR., PH.D.
Associate Professor of Ophthalmology
School of Medicine
Emory University
Atlanta, Georgia

WLADYSLAW J. MANSKI, PH.D.
Professor of Microbiology
Department of Ophthalmology
College of Physicians and Surgeons
Columbia University
New York, New York

IRENE H. MAUMENEE, M.D.
Assistant Professor of Ophthalmology
and of Medicine
Wilmer Ophthalmological Institute
School of Medicine
Johns Hopkins University
Baltimore, Maryland

JOHN W. PATTERSON, M.D., PH.D.
Professor of Physiology
School of Medicine
University of Connecticut
Farmington, Connecticut

ROBERT V. TAO, PH.D.
Research Assistant Professor
of Ophthalmology
College of Medicine
University of Illinois
Chicago, Illinois

SAMUEL VAINISI, D.V.M.
Assistant Professor of Ophthalmology
College of Medicine
University of Illinois
Chicago, Illinois

RUTH E. VAN HEYNINGEN, PH.D.
Nuffield Laboratory of Ophthalmology
University of Oxford
Oxford, England

SHAMBHU VARMA, PH.D.
Director of Ophthalmological
Research
School of Medicine
University of Maryland
Baltimore, Maryland

JACOB T. WILENSKY, M.D.
Associate Professor of Ophthalmology
College of Medicine
University of Illinois
Chicago, Illinois

SEYMOUR ZIGMAN, PH.D.
Associate Professor of
Ophthalmology and Biochemistry
Department of Surgery
School of Medicine and Dentistry
University of Rochester
Rochester, New York

Glaucoma

Chairman

W. MORTON GRANT, M.D.
David Glendenning Cogan Professor
of Ophthalmology
Harvard Medical School
Boston, Massachusetts

Members

DOUGLAS R. ANDERSON, M.D.
Associate Professor of Ophthalmology
School of Medicine
University of Miami
Miami, Florida

ELMER J. BALLINTINE, M.D.
Clinical Director
National Eye Institute
Bethesda, Maryland

BERNARD BECKER, M.D.
Professor and Head
Department of Ophthalmology
School of Medicine
Washington University
St. Louis, Missouri

MARVIN L. SEARS, M.D.
Chairman
Department of Ophthalmology
and Visual Sciences
School of Medicine
Yale University
New Haven, Connecticut

V. EVERETT KINSEY, PH.D.
(ex officio)
Director Emeritus
Institute of Biological Sciences
Oakland University
Rochester, Michigan

Consultants

A. ROBERT BELLOWS, M.D.
Clinical Instructor in Ophthalmology
Harvard Medical School
Boston, Massachusetts

RICHARD F. BRUBAKER, M.D.
Associate Consultant of Ophthalmology
Mayo Medical School
Rochester, Michigan

PAUL A. CHANDLER, M.D.
Associate Clinical Professor
of Ophthalmology, Retired
Harvard Medical School
Boston, Massachusetts

Chairman

W. MAXWELL COWAN, M.D., PH.D.
Professor and Chairman
Department of Anatomy
and Neurobiology
School of Medicine
Washington University
St. Louis, Missouri

Members

EMILIO BIZZI, M.D.
Professor of Psychology
Massachusetts Institute of
Technology
Cambridge, Massachusetts

NIGEL W. DAW, PH.D.
Professor of Physiology
and Biophysics
School of Medicine
Washington University
St. Louis, Missouri

DAVID H. HUBEL, M.D.
George Packer Berry Professor
of Neurobiology
Harvard Medical School
Boston, Massachusetts

ARTHUR JAMPOLSKY, M.D.
Director
The Smith-Kettlewell Institute
of Visual Sciences and
Department of Visual Sciences
University of the Pacific
San Francisco, California

DAVID A. ROBINSON, M.D.
Professor of Ophthalmology
and of Biomedical Engineering
Wilmer Ophthalmological Institute
School of Medicine
Johns Hopkins University
Baltimore, Maryland

GUNTER K. VON NOORDEN, M.D.
Professor of Ophthalmology
Baylor College of Medicine
Houston, Texas

GERALD WESTHEIMER, PH.D.
Professor of Physiology
University of California, Berkeley
Berkeley, California

JOHN LOTT BROWN, PH.D.
(ex officio)
Director
Center for Visual Sciences
University of Rochester
Rochester, New York

Consultants

DAVID G. COGAN, M.D.
Senior Staff Ophthalmologist
National Eye Institute
Bethesda, Maryland

WILLIAM F. HOYT, M.D.
Professor of Ophthalmology
School of Medicine
University of California,
San Francisco
San Francisco, California

SHIRLEY WRAY, M.D.
Associate Professor of Neurology
(Neurophthalmology)
Massachusetts General Hospital
Harvard Medical School
Boston, Massachusetts

Vision Research Training

Chairman

JOHN W. PATTERSON, M.D., PH.D.
Professor of Physiology
School of Medicine
University of Connecticut
Farmington, Connecticut

Members

HENRY F. EDELHAUSER, PH.D.
Professor of Physiology and Ophthalmology
School of Medicine
Medical College of Wisconsin
Milwaukee, Wisconsin

PAUL HENKIND, M.D., PH.D.
Professor and Chairman
Department of Ophthalmology
Montefiore Hospital and Medical Center
New York, New York

CLYDE W. OYSTER, O.D., PH.D.
Associate Professor of Physiological Optics
School of Optometry
University of Alabama
Birmingham, Alabama

WALTER N. SCOTT, M.D.
Associate Professor of Ophthalmology
Mount Sinai School of Medicine
New York, New York

VIVIAN C. SMITH, PH.D.
Research Associate
Eye Research Laboratories
University of Chicago
Chicago, Illinois

JOHN LOTT BROWN, PH.D.
(ex officio)
Director
Center for Visual Sciences
University of Rochester
Rochester, New York

Consultants

G. WINSTON BARBER, PH.D.
Chief
Department of Biochemistry
Wills Eye Hospital
Philadelphia, Pennsylvania

RICHARD F. BRUBAKER, M.D.
Associate Consultant of Ophthalmology
Mayo Medical School
Rochester, Michigan

ANN H. BUNT, PH.D.
Associate Professor of Ophthalmology
School of Medicine
University of Washington
Seattle, Washington

RONALD E. CARR, M.D.
Professor of Ophthalmology
School of Medicine
New York University
New York, New York

CLAES-HENRIK DOHLMAN, M.D.
Director and Senior Scientist
Department of Cornea Research
Eye Research Institute of Retina Foundation
Boston, Massachusetts, and
Professor and Chairman
Department of Ophthalmology
Massachusetts Eye and Ear Infirmary
Harvard Medical School
Boston, Massachusetts

CHRISTINA ENROTH-CUGELL, M.D., PH.D.
Professor of Electrical Engineering and Computer Science and of Biological Sciences
Technological Institute
Northwestern University
Evanston, Illinois

GEORGE B. HUTCHISON, M.D.
Professor of Epidemiology
Harvard School of Public Health
Boston, Massachusetts

ANTHONY B. NESBURN, M.D.
Head
Cornea and Virology Research Unit and
Associate Professor of Clinical
Ophthalmology
Estelle Doheny Eye Foundation
University of Southern California
Los Angeles, California

ARTHUR M. SILVERSTEIN, PH.D.
Professor of Ophthalmology
Wilmer Ophthalmological Institute
School of Medicine
Johns Hopkins University
Baltimore, Maryland

Acknowledgments

In addition to the Panel members and scientific consultants listed on the preceding pages, the National Advisory Eye Council wishes to convey its deep appreciation to Carl Kupfer, M.D., Director of the National Eye Institute, and the following members of the NEI staff for their assistance in the preparation of this report:

Project Director, Julian M. Morris
Deputy, Terrence Gillen

Scientific Liaison, William F. Raub, Ph.D.
Retinal and Choroidal Diseases, Bernard Wortman, Ph.D.
Corneal Diseases and *Cataract,* Luigi Giacometti, Ph.D.
Glaucoma, Samuel C. Rawlings, Ph.D., Ralph J. Helmsen, Ph.D.
Sensory and Motor Disorders of Vision, Michael F. Halasz, Ph.D.
Vision Research Training, Thomas C. O'Brien, Ph.D.

Management, Budget, and Administrative Support, Edward H. McManus, Francine Little, Phyllis McKee, Constance Miller, Karyn Ross, Donna Phillips

Grants and Contracts Information, Anna Marie Perrell, Carolyn McHale, Lucille Barnhouse, Carolyn Grimes, Brian Smith, Barbara Cawthon

Special thanks go to Elizabeth A. Brownell and Lynne M. Allen of the NEI Office of Program Planning and Scientific Reporting for their dedication and significant contributions in guiding this report through the publication process. Thanks also to Howard Bartner for medical illustrations, to Kappa Systems, Inc., for data collection and classification, to Linda M. Richardson for editorial support, and to Michael Olmert for typography and design.

DHEW Publication No. (NIH) 78-1258